BEST AVAILABLE IMAGES

115453

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

Requestor's Name: Rebecca Roth

Serial Number: 09/383,144

Date: 2/26/04

Phone: 308 4724

Art Unit: 1614

Rem 4C70

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

(1) Please search author John Arcade for his/her work. Also search

(2a) Rhodamine-123 in solution of ethyl alcohol

(2b) ethyl alc + sugar in IV solutions

(3) Solution of 2 to treat carcinoma of prostate cancer

(4) protocol of measuring PSA before & after chemo.

prostate-specific antigen

Thanks
Rebecca

RECEIVED
FEB 27 2004
STIC

STAFF USE ONLY

Date completed: 2-27-04

Searcher: [illegible]

Terminal time: 120

Elapsed time: 20 min

CPU time: _____

Total time: _____

Number of Searches: _____

Number of Databases: _____

Search Site

_____ STIC

_____ CM-1

_____ Pre-S

Type of Search

_____ N.A. Sequence

_____ A.A. Sequence

_____ Structure

/ Bibliographic

Vendors

_____ IG

3.89 STN

_____ Dialog

_____ APS

_____ Geninfo

_____ SDC

_____ DARC/Questel

_____ Other

PTO-1590 (9-90)

posttreatment prostate specific antigen (PSA) values were measured, and who had a minimum followup of 2 years. Outcome was analyzed in an actuarial fashion using clinical disease-free survival and biochemical disease-free survival (freedom from an increasing PSA level or a PSA level of greater than 1.0 ng./ml. 2 years following irradiation) as end points. Of the patients 54% achieved a post-irradiation nadir value in the range 0 to 1.0 ng./ml. and 29% had a nadir value that was undetectably low (less than 0.5 ng./ml.). The likelihood of achieving these values was greater among patients with early stage than locally advanced tumors. For all T stages the likelihood of being disease-free at 4 years was substantially and significantly lower when PSA was used as an end point than when clinical evaluation alone was used: stages T1 and T2 (85 patients) 41% versus 71%, and stages T3 and T4 (76 patients) 15% versus 61%. For the whole group at 4 years clinical control was 67% but biochemical control was only 26% ($p < 0.05$). The likelihood of being free of biochemical evidence of persistent disease at 4 years was a function of the initial PSA value (PSA less than 4.0 in 81% of the cases, 4.1 to 10.0 in 43%, 10.1 to 20.0 in 31%, 20.1 to 50.0 in 6% and greater than 50.0 in 0%). For stages T1 and T2 cancer patients with an initial PSA level of less than 15 ng./ml. (67% of all early stage cases) this value was 65% and it was even higher (73%) when poorly differentiated tumors were excluded. When the initial PSA level for stages T1 and T2 tumors was greater than 15 ng./ml. the projected 4-year rate of freedom from biochemical failure was only 7%. For stages T3 and T4 cancer patients the corresponding figures were 39% for those with an initial PSA level of less than 15 ng./ml. and 0% for those with an initial PSA level of greater than 15 ng./ml. The prognostic power of the initial PSA level was independent of stage, grade, patient age and prior transurethral resection of the prostate in a multivariate analysis. An initial serum PSA level of more than 15 ng./ml. is, therefore, a powerful predictor of probable failure with conventional radiation therapy. Serum PSA monitoring is a sensitive detector of early relapse.(ABSTRACT TRUNCATED AT 400 WORDS)

L137 ANSWER 29 OF 29 MEDLINE on STN
ACCESSION NUMBER: 93172422 MEDLINE
DOCUMENT NUMBER: 93172422 PubMed ID: 7679756
TITLE: Prostate specific antigen after external beam radiotherapy for prostatic cancer: followup.
AUTHOR: Kaplan I D; Cox R S; Bagshaw M A
CORPORATE SOURCE: Department of Radiation Oncology, Stanford University Medical Center, California.
SOURCE: JOURNAL OF UROLOGY, (1993 Mar) 149 (3) 519-22.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930402
Last Updated on STN: 19960129
Entered Medline: 19930322

AB Between 1986 and 1989, 117 patients with **pretreatment** and serial posttreatment prostate specific antigen values received external beam radiotherapy at our hospital. Followup ranged from 0.6 to 5.9 years (mean 2.7). No patient had hormonal manipulation before distant recurrence. Biochemical relapse, defined as an increasing prostate specific antigen level after treatment, was observed in 44 patients. To date 30 of these 44 patients (68%) have had clinical relapse. The prognostic factors of advanced local stage, high Gleason score and high elevations of **pretreatment** prostate specific antigen values predicted for biochemical relapse and subsequent clinical failure. The interval between biochemical and clinical relapse was 156 +/- 46 days. Biochemical relapse is an important end point that can be used to determine the effect of

DOCUMENT NUMBER: 94324125 PubMed ID: 7519382
TITLE: Post-therapy change in prostate-specific antigen levels as a clinical trial endpoint in hormone-refractory prostatic cancer: a trial with 10-ethyl-deaza-aminopterin.
AUTHOR: Schultz P K; Kelly W K; Begg C; Liebertz C; Cohen L; Scher H I
CORPORATE SOURCE: Department of Medicine, Memorial-Sloan-Kettering Cancer Center, New York, New York.
CONTRACT NUMBER: NCI CA-05826 (NCI)
NCI CA-09207-14 (NCI)
NCI CM-57732 (NCI)
SOURCE: UROLOGY, (1994 Aug) 44 (2) 237-42.
Journal code: 0366151. ISSN: 0090-4295.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940909
Last Updated on STN: 19960129
Entered Medline: 19940826

AB OBJECTIVES. Serial changes in prostate-specific antigen (PSA) correlate with disease status in all stages of prostatic cancer. For hormone-refractory disease, post-therapy declines of 50% and 80% from baseline are associated with an improved survival. This study sought to evaluate edatrexate, a synthetic antifolate, in hormone-refractory prostatic cancer using post-therapy PSA change as the initial endpoint. METHODS. Fourteen patients with progression of disease despite castrate levels of testosterone received edatrexate. Serial changes in PSA were monitored and correlated with other parameters of outcome. RESULTS. Stabilization of a rising PSA level in parallel with clinical stabilization of disease was observed in one patient; disease in all others progressed. Toxic reactions were acceptable. CONCLUSIONS. With no objective evidence for antitumor activity as assessed by post-therapy PSA changes in any of the patients treated, edatrexate seems a poor candidate for future study. The use of post-therapy PSA change as the initial screening modality allows treatments to be evaluated rapidly in patients without measurable disease. The methodology proposed will require validation in prospective phase III investigations using survival as the endpoint.

L137 ANSWER 28 OF 29 MEDLINE on STN
ACCESSION NUMBER: 94142016 MEDLINE
DOCUMENT NUMBER: 94142016 PubMed ID: 7508522
TITLE: Radical radiation therapy in the management of prostatic adenocarcinoma: the initial prostate specific antigen value as a predictor of treatment outcome.
AUTHOR: Zietman A L; Coen J J; Shipley W U; Willett C G; Efird J T
CORPORATE SOURCE: Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston 02114.
SOURCE: JOURNAL OF UROLOGY, (1994 Mar) 151 (3) 640-5.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 19960129
Entered Medline: 19940314

AB We studied 161 prostate cancer patients treated by radical irradiation alone without endocrine therapy in whom **pretreatment** and

posttreatment prostate specific antigen (PSA) values were measured, and who had a minimum followup of 2 years. Outcome was analyzed in an actuarial fashion using clinical disease-free survival and biochemical disease-free survival (freedom from an increasing PSA level or a PSA level of greater than 1.0 ng./ml. 2 years following irradiation) as end points. Of the patients 54% achieved a post-irradiation nadir value in the range 0 to 1.0 ng./ml. and 29% had a nadir value that was undetectably low (less than 0.5 ng./ml.). The likelihood of achieving these values was greater among patients with early stage than locally advanced tumors. For all T stages the likelihood of being disease-free at 4 years was substantially and significantly lower when PSA was used as an end point than when clinical evaluation alone was used: stages T1 and T2 (85 patients) 41% versus 71%, and stages T3 and T4 (76 patients) 15% versus 61%. For the whole group at 4 years clinical control was 67% but biochemical control was only 26% ($p < 0.05$). The likelihood of being free of biochemical evidence of persistent disease at 4 years was a function of the initial PSA value (PSA less than 4.0 in 81% of the cases, 4.1 to 10.0 in 43%, 10.1 to 20.0 in 31%, 20.1 to 50.0 in 6% and greater than 50.0 in 0%). For stages T1 and T2 cancer patients with an initial PSA level of less than 15 ng./ml. (67% of all early stage cases) this value was 65% and it was even higher (73%) when poorly differentiated tumors were excluded. When the initial PSA level for stages T1 and T2 tumors was greater than 15 ng./ml. the projected 4-year rate of freedom from biochemical failure was only 7%. For stages T3 and T4 cancer patients the corresponding figures were 39% for those with an initial PSA level of less than 15 ng./ml. and 0% for those with an initial PSA level of greater than 15 ng./ml. The prognostic power of the initial PSA level was independent of stage, grade, patient age and prior transurethral resection of the prostate in a multivariate analysis. An initial serum PSA level of more than 15 ng./ml. is, therefore, a powerful predictor of probable failure with conventional radiation therapy. Serum PSA monitoring is a sensitive detector of early relapse.(ABSTRACT TRUNCATED AT 400 WORDS)

L137 ANSWER 29 OF 29 MEDLINE on STN
ACCESSION NUMBER: 93172422 MEDLINE
DOCUMENT NUMBER: 93172422 PubMed ID: 7679756
TITLE: Prostate specific antigen after external beam radiotherapy for prostatic cancer: followup.
AUTHOR: Kaplan I D; Cox R S; Bagshaw M A
CORPORATE SOURCE: Department of Radiation Oncology, Stanford University Medical Center, California.
SOURCE: JOURNAL OF UROLOGY, (1993 Mar) 149 (3) 519-22.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930402
Last Updated on STN: 19960129
Entered Medline: 19930322

AB Between 1986 and 1989, 117 patients with **pretreatment** and serial posttreatment prostate specific antigen values received external beam radiotherapy at our hospital. Followup ranged from 0.6 to 5.9 years (mean 2.7). No patient had hormonal manipulation before distant recurrence. Biochemical relapse, defined as an increasing prostate specific antigen level after treatment, was observed in 44 patients. To date 30 of these 44 patients (68%) have had clinical relapse. The prognostic factors of advanced local stage, high Gleason score and high elevations of **pretreatment** prostate specific antigen values predicted for biochemical relapse and subsequent clinical failure. The interval between biochemical and clinical relapse was 156 +/- 46 days. Biochemical relapse is an important end point that can be used to determine the effect of

treatment in prostatic cancer research.

FILE 'HOME' ENTERED AT 14:34:11 ON 27 FEB 2004

ANSWER 115 OF 42399 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 94148842 EMBASE

DN 1994148842

TI Parenteral formulation development of renin inhibitor Abbott-72517.

AU Gupta S.L.; Patel J.P.; Jones D.L.; Partipilo R.W.

CS Clinical Center Pharmacy Department, NIH, Bldg 10, 9000 Rockville Pike,Bethesda, MD 20892, United States

SO PDA Journal of Pharmaceutical Science and Technology, (1994) 48/2 (86-91). ISSN: 0279-7976 CODEN: JPHTEU

CY United States

DT Journal; Article

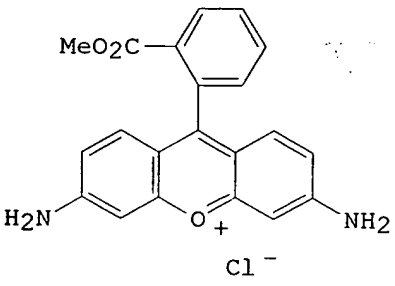
FS 027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB Abbott-72517 is an inhibitor of human renin and is being investigated for the treatment of hypertension. It is an orally bioavailable candidate which is being developed for oral as well as **intravenous** use. The preclinical development of this molecule involved studies to evaluate irritation at the site of injection in an animal model. Several formulation variables such as drug concentration, types of buffer (citrate or acetate), addition of **cosolvent** (**ethanol**) to enhance drug solubility, and tonicity modifiers such as glycerin or mannitol were evaluated. Additionally, in vitro formulation- whole blood hemolysis and plasma precipitation studies were conducted. Based on these studies, a liquid formulation containing 1.2 mg/mL Abbott-72517·HCl as base, 0.01M citrate buffer, pH 3.7, in 0.45% sodium chloride containing 2.5% mannitol was recommended for preclinical studies. Various processing and administration parameters were evaluated including filter qualification and compatibility of the drug with typical infusion fluids and administration sets. The liquid formulation was further characterized for physical and chemical stability. It was shown that it has acceptable stability at ambient temperature. Based on the accelerated temperature storage results, T90 at 25°C is > 1 year for the ready-to-use liquid formulation. Additionally, a lyophilized version of the liquid formulation was evaluated.

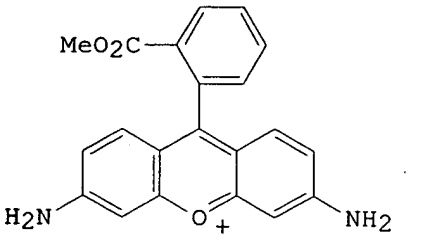
AN 1983:587241 CAPLUS
DN 99:187241
TI Anticarcinoma activity in vivo of **rhodamine 123**, a mitochondrial-specific dye
AU Bernal, Samuel D.; Lampidis, Theodore J.; McIsaac, Robert M.; Chen, Lan Bo
CS Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SO Science (Washington, D. C., 1883-) (1983), 222(4620), 169-72
CODEN: SCIEAS; ISSN: 0036-8075
DT Journal
LA English
CC 1-6 (Pharmacology)
GI



I

AB **Rhodamine 123** (I) [62669-70-9] exhibited anticarcinoma activity in mice with various exptl. **carcinomas**, and this activity was potentiated by 2-deoxyglucose [154-17-6].
ST anticarcinoma **rhodamine 123**
IT Neoplasm inhibitors
(**carcinoma, rhodamine 123**)
IT 154-17-6
RL: BIOL (Biological study)
(**carcinoma** inhibition by **rhodamine 123** potentiation by)
IT 62669-70-9
RL: BIOL (Biological study)
(**carcinoma** inhibition by, deoxyglucose potentiation of)

AN 1983:587241 CAPLUS
DN 99:187241
TI Anticarcinoma activity in vivo of **rhodamine 123**, a mitochondrial-specific dye
AU Bernal, Samuel D.; Lampidis, Theodore J.; McIsaac, Robert M.; Chen, Lan Bo
CS Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SO Science (Washington, D. C., 1883-) (1983), 222(4620), 169-72
CODEN: SCIEAS; ISSN: 0036-8075
DT Journal
LA English
CC 1-6 (Pharmacology)
GI



I

AB **Rhodamine 123** (I) [62669-70-9] exhibited anticarcinoma activity in mice with various exptl. **carcinomas**, and this activity was potentiated by 2-deoxyglucose [154-17-6].
ST anticarcinoma **rhodamine 123**
IT Neoplasm inhibitors
(**carcinoma, rhodamine 123**)
IT 154-17-6
RL: BIOL (Biological study)
(**carcinoma** inhibition by **rhodamine 123** potentiation by)
IT 62669-70-9
RL: BIOL (Biological study)
(**carcinoma** inhibition by, deoxyglucose potentiation of)

```
=> fil capl; d que l3
FILE 'CAPLUS' ENTERED AT 14:27:24 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 27 Feb 2004  VOL 140 ISS 10
FILE LAST UPDATED: 26 Feb 2004  (20040226/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L1            13 SEA FILE=CAPLUS ABB=ON  ARCADI J?/AU
L2        352163 SEA FILE=CAPLUS ABB=ON  NEOPLAS?/OBI
L3             6 SEA FILE=CAPLUS ABB=ON  L1 AND L2


=> fil medl; d que l59

FILE 'MEDLINE' ENTERED AT 14:27:24 ON 27 FEB 2004

 FILE LAST UPDATED: 25 FEB 2004 (20040225/UP).  FILE COVERS 1958 TO DATE.

 On December 14, 2003, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description
 on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L55           26 SEA FILE=MEDLINE ABB=ON  ARCADI J?/AU
L57          868 SEA FILE=MEDLINE ABB=ON  RHODAMINE 123/CT
L59            4 SEA FILE=MEDLINE ABB=ON  L55 AND L57


=> fil embase; d que l93

FILE 'EMBASE' ENTERED AT 14:27:25 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

 FILE COVERS 1974 TO 26 Feb 2004 (20040226/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.
```

This file contains CAS Registry Numbers for easy and accurate substance identification.

L89 13 SEA FILE=EMBASE ABB=ON ARCADI J?/AU
L90 1247 SEA FILE=EMBASE ABB=ON RHODAMINE 123/CT
L93 4 SEA FILE=EMBASE ABB=ON L89 AND L90

=> fil drugu;d que l105; fil wpids; d que l120

FILE 'DRUGU' ENTERED AT 14:27:26 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE LAST UPDATED: 25 FEB 2004 <20040225/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001. <<<
>>> (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION <<<
>>> SEE HELP COST <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

L105 6 SEA FILE=DRUGU ABB=ON ARCADI J?/AU

FILE 'WPIDS' ENTERED AT 14:27:26 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE LAST UPDATED: 26 FEB 2004 <20040226/UP>
MOST RECENT DERWENT UPDATE: 200414 <200414/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE http://thomsonderwent.com/coverage/latestupdates/ <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://thomsonderwent.com/support/userguides/ <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM DERWENT UPDATE 200403.
THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.
SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<

L120 1 SEA FILE=WPIDS ABB=ON ARCADI J?/AU

=> dup rem l59,l105,l3,l93,l120

FILE 'MEDLINE' ENTERED AT 14:27:28 ON 27 FEB 2004

FILE 'DRUGU' ENTERED AT 14:27:28 ON 27 FEB 2004

FILE 'CAPLUS' ENTERED AT 14:27:28 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'EMBASE' ENTERED AT 14:27:28 ON 27 FEB 2004

FILE 'WPIDS' ENTERED AT 14:27:28 ON 27 FEB 2004

PROCESSING COMPLETED FOR L59
PROCESSING COMPLETED FOR L105
PROCESSING COMPLETED FOR L3
PROCESSING COMPLETED FOR L93
PROCESSING COMPLETED FOR L120
L123 14 DUP REM L59 L105 L3 L93 L120 (7 DUPLICATES REMOVED)
ANSWERS '1-4' FROM FILE MEDLINE
ANSWERS '5-9' FROM FILE DRUGU
ANSWERS '10-13' FROM FILE CAPLUS
ANSWER '14' FROM FILE EMBASE

=> d ibib ed ab hitrn 1-14

L123 ANSWER 1 OF 14 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 1999032304 MEDLINE
DOCUMENT NUMBER: 99032304 PubMed ID: 9817392
TITLE: The effect of rhodamine-123 on 3 prostate tumors from the rat.
AUTHOR: **Arcadi J A**
CORPORATE SOURCE: Huntington Medical Research Institutes, Pasadena, California, USA.
SOURCE: JOURNAL OF UROLOGY, (1998 Dec) 160 (6 Pt 2) 2402-6.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981211
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981211
AB PURPOSE: Rhodamine-123 (Rh-123) was found to have a specific attraction to the mitochondria of tumor cells. The destruction of rat prostate tumor cells by Rh-123 is described. MATERIALS AND METHODS: Tissue was used from rat prostate studies of Rh-123 treatment of R3327-H, PA III prostate tumor of Pollard and the autochthonous tumor in Lobund-Wistar rats. All tissues were fixed in 10% buffered formalin, paraffin embedded and sectioned at 1 to 3 micron. for good cellular detail. RESULTS: Destructive processes were seen in all 3 rat prostate tumor models evaluated. The changes included acinar cell clumping, acinar destruction with scarring, cyst formation within acinar cells and increased stromal cells. CONCLUSIONS: Since all tumor models were found to respond to Rh-123 in a similar manner, any of them could be used for the evaluation of anticancer agents. These studies demonstrated that Rh-123 was effective in suppressing the growth of hormone sensitive and insensitive rat prostate tumor cells.

L123 ANSWER 2 OF 14 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 95295308 MEDLINE
DOCUMENT NUMBER: 95295308 PubMed ID: 7776658
TITLE: Studies of rhodamine-123: effect on rat prostate cancer and human prostate cancer cells in vitro.
AUTHOR: **Arcadi J A**; Narayan K S; Techy G; Ng C P; Saroufeem R M; Jones L W
CORPORATE SOURCE: Huntington Medical Research Institutes, Pasadena, CA 91101, USA.
SOURCE: JOURNAL OF SURGICAL ONCOLOGY, (1995 Jun) 59 (2) 86-92; discussion 92-3.
Journal code: 0222643. ISSN: 0022-4790.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950720
Last Updated on STN: 19990129
Entered Medline: 19950711
ED Entered STN: 19950720
Last Updated on STN: 19990129
Entered Medline: 19950711
AB The effect of the lipophilic, cationic dye, Rhodamine-123 (Rh-123), on prostate cancer in rats, and on three tumor cell lines in vitro is reported here. The general toxicity of Rh-123 in mice has been found to be minimal. Lobund-Wistar (L-W) rats with the autochthonous prostate cancer of Pollard were treated for six doses with Rh-123 at a dose of 15 mg/kg subcutaneously every other day. Microscopic examination of the tumors revealed cellular and acinar destruction. The effectiveness of Rh-123 as a cytotoxic agent was tested by clonogenic and viability assays in vitro with three human prostate cancer cell lines. Severe (60-95%) growth inhibition was observed following Rh-123 exposure for 2-5 days at doses as low as 1.6 micrograms/ml in all three prostate cancer cell lines.

L123 ANSWER 3 OF 14 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 90286634 MEDLINE
DOCUMENT NUMBER: 90286634 PubMed ID: 2355740
TITLE: Use of rhodamine 123 in the treatment of the Pollard III rat prostate adenocarcinoma.
AUTHOR: **Arcadi J A**
CORPORATE SOURCE: Cancer Research Laboratory, Whittier College, CA 90608.
SOURCE: JOURNAL OF SURGICAL ONCOLOGY, (1990 Jun) 44 (2) 103-8.
Journal code: 0222643. ISSN: 0022-4790.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199007
ENTRY DATE: Entered STN: 19900824
Last Updated on STN: 19990129
Entered Medline: 19900720
ED Entered STN: 19900824
Last Updated on STN: 19990129
Entered Medline: 19900720
AB Significant destruction of the Pollard III rat prostate adenocarcinoma was achieved by treatment with rhodamine 123 at a dosage of 15 mg/kg every other day for 33 to 38 days. Injection of tumor remnants into untreated animals produced no tumor regrowth. Our data have demonstrated rhodamine 123 to be a significant drug for the management of the very aggressive Pollard III tumor.

L123 ANSWER 4 OF 14 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 87071383 MEDLINE
DOCUMENT NUMBER: 87071383 PubMed ID: 3787924
TITLE: Rhodamine-123 as effective agent in rat prostate tumor R3327-H. Preliminary report.
AUTHOR: **Arcadi J A**
SOURCE: UROLOGY, (1986 Dec) 28 (6) 501-3.
Journal code: 0366151. ISSN: 0090-4295.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198701
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19990129
Entered Medline: 19870120
ED Entered STN: 19900302
Last Updated on STN: 19990129
Entered Medline: 19870120
AB Rhodamine-123 is a fluorescent dye that preferentially stains mitochondria and causes damage to mitochondria of malignant cells. The effect of this mitochondriacide on the transplantable rat prostate tumor R3327-H was determined in this study. Rhodamine was administered subcutaneously every other day at a dosage of 15 mg/Kg body weight for fifty-two days. There was significant alteration of the acinar cells with disruption of the cells from the basement membrane, as well as vacuolization and change in fibroblast shape and density. Rhodamine-123 may have a role in the treatment of prostatic cancer.

L123 ANSWER 5 OF 14 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1997-39581 DRUGU P
TITLE: Comparative cytotoxicity of rhodamine 123 and MKT-077 on prostate cancer and non-tumorigenic cells in vitro.
AUTHOR: Shankar Narayan K; Carl J; **Arcadi J A**; Jones L W
CORPORATE SOURCE: Huntington-Med.Res.Inst.
LOCATION: Pasadena, Cal., USA
SOURCE: Proc.Am.Assoc.Cancer Res. (38, 88 Meet., 220, 1997) ISSN: 0197-016X
AVAIL. OF DOC.: Huntington Medical Research Institutes, Pasadena, CA 91101, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The cytotoxicity of MKT-077 (Sandoz) was compared with that of rhodamine 123 (Rh123) against 2 human prostate cancer (PC-3, DU-145) and 2 non-tumorigenic (NPF-209 prostate, NF-2 foreskin) fibroblast cell-lines maintained in-vitro. (conference abstract).

L123 ANSWER 6 OF 14 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1988-21677 DRUGU T
TITLE: Parenteral Globulin in the Management of Urinary Tract Infections.
AUTHOR: **Arcadi J A**
LOCATION: Whittier, California, United States
SOURCE: J.Urol. (139, No. 4, Pt. 2, 397A, 1988) 2 Ref.
CODEN: JOURAA ISSN: 0022-5347
AVAIL. OF DOC.: No Reprint Address.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB I.m. or intrafat (s.c.) injections of an immune globulin preparation produced abatement of infection in a study on 8 patients with recurrent

urinary tract infections. No adverse effects were reported. (congress abstract).

L123 ANSWER 7 OF 14 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1988-20660 DRUGU P
TITLE: Rhodamine-123 is a Significant Agent to Control Adenocarcinoma of the Prostate of the Rat.
AUTHOR: **Arcadi J A**
LOCATION: Whittier, California, United States
SOURCE: J.Urol. (139, No. 4, Pt. 2, 175A, 1988) 1 Ref.
CODEN: JOURAA ISSN: 0022-5347
AVAIL. OF DOC.: No Reprint Address.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Prostate-tumor-bearing rats were treated by orchidectomy, testosterone implant, rhodamine-123 or a combination of all 3. Results strongly indicate that rhodamine-123 destroys cells by mitochondrial destruction associated with aneurysm-like dilatation. Rhodamine-123 may be an effective agent in the management of prostate carcinoma in man. (congress abstract).

L123 ANSWER 8 OF 14 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1987-22808 DRUGU P
TITLE: The Effect of Rhodamine-123 on the R-3372-H Prostate Tumor and on the Tissues of the Rat Bearing That Tumor.
AUTHOR: **Arcadi J A**
LOCATION: Whittier, California, United States
SOURCE: J.Urol. (137, No. 4, Pt. 2, 369A, 1987)
CODEN: JOURAA ISSN: 0022-5347
AVAIL. OF DOC.: No Reprint Address.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Ultrastructural changes in mitochondria of rats with Dunning-R-3327-H prostate adenocarcinomas were studied following chronic administration of Rhodamine-123 via osmotic pumps. Short pulsatile doses (pellet implantation or daily injections) of Rhodamine-123 resulted in the destruction of the tumors. It was concluded that Rhodamine-123 is a potent antitumor agent for the R-3327-H rat prostate cancer, and its use in man seems possible. (congress abstract).

L123 ANSWER 9 OF 14 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1986-26620 DRUGU P
TITLE: Rhodamine-123: Effect on Rat Prostate Tumor, R3327H, a Preliminary Report.
AUTHOR: **Arcadi J A**
LOCATION: Whittier, California, United States
SOURCE: J.Urol. (135, No. 4, Pt. 2, 337A, 1986)
CODEN: JOURAA ISSN: 0022-5347
AVAIL. OF DOC.: No Reprint Address.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB IN rats bearing s.c. R3327H prostate tumors, s.c. rhodamine-123 decreased the size of the tumors by destroying tumor cell mitochondria. (congress abstract).

L123 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 1997:281046 CAPLUS

DOCUMENT NUMBER: 126:268523
TITLE: Rhodamine 123 compositions and methods for treating prostate cancer
INVENTOR(S): **Arcadi, John Albert**
PATENT ASSIGNEE(S): Huntington Medical Research Institute, USA
SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 761216	A1	19970312	EP 1996-305836	19960808
EP 761216	B1	20031112		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 253908	E	20031115	AT 1996-305836	19960808
CA 2183015	AA	19970217	CA 1996-2183015	19960809
AU 9662071	A1	19970220	AU 1996-62071	19960813
JP 09110724	A2	19970428	JP 1996-233697	19960816
BR 9603454	A	19980512	BR 1996-3454	19960816

PRIORITY APPLN. INFO.: US 1995-516004 A 19950816
ED Entered STN: 02 May 1997
AB Prostate cancer in a patient is treated by administration of Rhodamine 123 orally or by i.v. injection of a treatment soln. of Rhodamine 123, EtOH, dextrose, and water in an amt. sufficient to effect in vivo destruction of prostate cancer cells. The treatment soln. is made by mixing a stock soln. of Rhodamine 123 in EtOH-H2O (95:5 by vol.) with a soln. of 5 wt.% dextrose in water. Treatment can be monitored by measuring the level of prostate-specific antigen in the blood of the patient.

L123 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1981:28594 CAPLUS
DOCUMENT NUMBER: 94:28594
TITLE: Cytochemical localization of lipid, peroxidase, and carbohydrate substances in the Dunning prostatic adenocarcinoma R3327H: an ultrastructural analysis
AUTHOR(S): **Arcadi, John A.**
CORPORATE SOURCE: Dep. Biol., Whittier Coll., Whittier, CA, USA
SOURCE: Journal of Surgical Oncology (1980), 15(3), 287-96
CODEN: JSONAU; ISSN: 0022-4790
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 1984
AB The ultrastructural organization of the cells of the transplantable prostatic adenocarcinoma of the rat, R3327H, was studied on a cytochem. level. There were, in the tumor cells and not in normal prostatic epithelial cells, lipid compartments with an intense peroxidase membrane. The lipid droplet was compartmentalized by concanavalin A-pos. material. Apparently, this tumor cell may be a degenerating or old cell. It may be that this cancer is a disease of dying cells, the degrading consequence of cell growth.

L123 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1972:54674 CAPLUS
DOCUMENT NUMBER: 76:54674
TITLE: Mast cells in the estrogen-induced transplantable renal tumor of the hamster
AUTHOR(S): **Arcadi, John A.**
CORPORATE SOURCE: Dep. Biol., Whittier Coll., Whittier, CA, USA
SOURCE: Journal of Surgical Oncology (1971), 3(5), 553-7

CODEN: JSONAU; ISSN: 0022-4790
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 1984
AB Mast cells were seen in great numbers in the transplantable estrogen-induced renal tumor of the hamster only when the tissue was frozen in isopentane cooled with liq. N at -155.deg. and cut on a cryostat at -20.deg.. Thus the method of tissue prepn. was very important when studying these cells.

L123 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1965:38240 CAPLUS
DOCUMENT NUMBER: 62:38240
ORIGINAL REFERENCE NO.: 62:6770e-g
TITLE: Glycogen-containing cells in estrogen-induced kidney tumors in hamster
AUTHOR(S): **Arcadi, John A.**
CORPORATE SOURCE: Whittier-Coll., Whittier, CA
SOURCE: Science (Washington, DC, United States) (1963), 142, 592-3
From: CZ 1964(27), Abstr. No. 1100.
CODEN: SCIEAS; ISSN: 0036-8075
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Apr 2001
AB Male hamster treated with stilbestrol and subpannicularly inoculated with Kirkman tumors developed autonomous and estrogen-dependent tumors. Both were frozen, after isolation, in isopentane at -155.degree. and kept at -70 for 7 days in abs. alc. with 1% Hg2Cl2. The tissue embedded in paraffin was sliced, the paraffin removed with petr. ether and the slices placed in abs. alc. One portion was placed in a 0.1% diastase soln. at pH 7 for 1-2 hrs. at 30, another portion was placed in buffer alone, a 3rd portion in abs. alc. They were stained by means of periodic acid-Schiff (PAS) reaction, and counter-stained with malachite green. Purple red granules were in connective tissue and in the tumor cells. Most of the cells were neg. to PAS. There was no staining by PAS in cells treated by diastase. Cells contg. glycogen were found in both tumors.

L123 ANSWER 14 OF 14 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999359103 EMBASE
TITLE: The effect of rhodamine-123 on 3 prostate tumors from the rat.
AUTHOR: **Arcadi J.A.**
CORPORATE SOURCE: J.A. Arcadi, Huntington Med. Research Institutes, Pasadena, CA, United States
SOURCE: Journal of Urology, (1999) 160/6 II (2402-2406).
Refs: 13
ISSN: 0022-5347 CODEN: JOURAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 028 Urology and Nephrology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Purpose: Rhodamine-123 (Rh-123) was found to have a specific attraction to the mitochondria of tumor cells. The destruction of rat prostate tumor cells by Rh-123 is described. Materials and Methods: Tissue was used from rat prostate studies of Rh-123 treatment of R3327-H, PA III prostate tumor of Pollard and the autochthonous tumor in Lobund-Wistar rats. All tissues were fixed in 10% buffered formalin, paraffin embedded and sectioned at 1 to 3 .mu. for good cellular detail. Results: Destructive processes were seen in all 3 rat prostate tumor models evaluated. The changes included

acinar cell clumping, acinar destruction with scarring, cyst formation within acinar cells and increased stromal cells. Conclusions: Since all tumor models were found to respond to Rh-123 in a similar manner, any of them could be used for the evaluation of anticancer agents. These studies demonstrated that Rh-123 was effective in suppressing the growth of hormone sensitive and insensitive rat prostate tumor cells.

```
=> fil capl; d que 18; d que 118
FILE 'CAPLUS' ENTERED AT 14:28:34 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 27 Feb 2004  VOL 140 ISS 10
FILE LAST UPDATED: 26 Feb 2004  (20040226/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L4             1 SEA FILE=REGISTRY ABB=ON  "RHODAMINE 123"/CN
L5             1 SEA FILE=REGISTRY ABB=ON  ETHANOL/CN
L6           623 SEA FILE=CAPLUS ABB=ON  L4
L7        166693 SEA FILE=CAPLUS ABB=ON  L5
L8             3 SEA FILE=CAPLUS ABB=ON  L6 AND L7



L2        352163 SEA FILE=CAPLUS ABB=ON  NEOPLAS?/OBI
L4             1 SEA FILE=REGISTRY ABB=ON  "RHODAMINE 123"/CN
L6           623 SEA FILE=CAPLUS ABB=ON  L4
L15       523788 SEA FILE=CAPLUS ABB=ON  (ETOH OR ETHYL ALCOHOL OR ETHANOL)/BI
L16           10 SEA FILE=CAPLUS ABB=ON  L6 AND L15
L18            2 SEA FILE=CAPLUS ABB=ON  L16 AND L2


=> s (18 or 118) not 13

L124           4 (L8 OR L18) NOT (L3) previously printed

=> fil medl; d que 162; fil embase; d que 192

FILE 'MEDLINE' ENTERED AT 14:28:36 ON 27 FEB 2004

 FILE LAST UPDATED: 25 FEB 2004 (20040225/UP).  FILE COVERS 1958 TO DATE.

 On December 14, 2003, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description
 on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
```

```
L57          868 SEA FILE=MEDLINE ABB=ON  RHODAMINE 123/CT
L61        47184 SEA FILE=MEDLINE ABB=ON  ETHANOL/CT
L62            0 SEA FILE=MEDLINE ABB=ON  L57 AND L61


FILE 'EMBASE' ENTERED AT 14:28:36 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

 FILE COVERS 1974 TO 26 Feb 2004 (20040226/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L90         1247 SEA FILE=EMBASE ABB=ON  RHODAMINE 123/CT
L92            3 SEA FILE=EMBASE ABB=ON  L90(L)IV/CT
```

IV = intravenous drug administration

```
=> s l92 not l93

L125           3 L92 NOT (L93)
```

previously printed

```
=> dup rem l124,l125
FILE 'CAPLUS' ENTERED AT 14:28:47 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 14:28:47 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.
PROCESSING COMPLETED FOR L124
PROCESSING COMPLETED FOR L125
L126           7 DUP REM L124 L125 (0 DUPLICATES REMOVED)
                 ANSWERS '1-4' FROM FILE CAPLUS
                 ANSWERS '5-7' FROM FILE EMBASE

=> d ibib ed ab hitrn 1-7

L126 ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1996:398785  CAPLUS
DOCUMENT NUMBER:          125:107162
TITLE:                    A combination of fluorescent probes for evaluation of
                          cytotoxicity and toxic mechanisms in isolated rainbow
                          trout hepatocytes
AUTHOR(S):                Lilius, H.; Haestbacka, T.; Isomaa, B.
CORPORATE SOURCE:         Department Biology, Aabo Akademi University,
                          Turku/Abo, FIN-20520, Finland
SOURCE:                   Toxicology in Vitro (1996), 10(3), 341-348
                          CODEN: TIVIEQ; ISSN: 0887-2333
PUBLISHER:                Elsevier
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
ED   Entered STN:  11 Jul 1996
AB   The toxicity of 17 chems. to freshly isolated rainbow trout hepatocytes
     was detd. using four different fluorescent probes measuring different
     endpoints.  Calcein was used to det. viability of the cells, rhodamine 123
     and 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine
     iodide (JC-1) to monitor mitochondrial activity and 5-
```

chloromethylfluorescein diacetate (CMFDA) to monitor intracellular glutathione (GSH) levels. An EC50 value 10 times lower than that obtained with the calcein assay was taken to indicate a specific action. Two sets of test chems. were used. The first set contained five chems. with a known specific toxic action and two chems. without a known main specific action at a cellular level, and this set was used to examine the specificity of the probes. The second set consisted of 10 chems. from the MEIC (Multicenter Evaluation of In Vitro Cytotoxicity) chem. list and included only oe chem. with a known main specific action at a cellular level. In the first set of chems. the CMFDA assay detected all chems. with known GSH-depleting action, and the results obtained with the second set of chems. indicated that none of the chems. act mainly by GSH depletion. However, the CMFDA assay showed one false pos. (antimycin-A). The results obtained with the rhodamine 123 and the JC-1 assay were less clear. The rhodamine 123 assay recognized the three chems. in set 1 interfering with mitochondrial function but gave one false pos. (ethanol) in this set, whereas the JC-1 assay recognized only two of the chems. and gave one false pos. (menadione). Both assays failed to detect the only chem. in set 2 with a known action on mitochondria (KCN). The authors conclude that calcein and CMFDA are good candidates as fluorometric probes for detection fo cell viability and depletion of GSH, resp. However, rhodamine 123 and JC-1, on the other hand, do not appear to be good probes for screening of mitochondrial activity in rainbow trout hepatocytes.

IT **64-17-5**, Ethanol, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (fluorescent probes for evaluation of cytotoxicity and toxic mechanisms in isolated rainbow trout hepatocytes)

IT **62669-70-9**, Rhodamine 123
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses) (fluorescent probes for evaluation of cytotoxicity and toxic mechanisms in isolated rainbow trout hepatocytes)

L126 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:96151 CAPLUS
DOCUMENT NUMBER: 124:197239
TITLE: Phototoxicity of some bromine-substituted rhodamine dyes: synthesis, photophysical properties and application as photosensitizers
AUTHOR(S): Pal, PRabir; Zeng, Hualing; Durocher, Gilles; Girard, Denis; Li, Tiechao; Gupta, Ajay K.; Giasson, Richard; Blanchard, Louise; Gaboury, Louis; et al.
CORPORATE SOURCE: Lab. Photophys. Mol., Univ. Montreal, Montreal, QC, Can.
SOURCE: Photochemistry and Photobiology (1996), 63(2), 161-8
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 15 Feb 1996
AB The synthesis of some bromine-substituted rhodamine derivs., viz., 4,5-dibromorhodamine Me ester (dye 2) and 4,5-dibromorhodamine Bu ester (dye 3), are reported. These dyes were synthesized to promote a more efficient cancer cell photosensitizer for potential use in in vitro bone marrow purging in prepn. for autologous bone marrow transplantation. Spectroscopic and photophys. characterization of these dyes together with rhodamine 123 (dye 1) are reported in water, methanol, **ethanol** and also in a microheterogeneous system, sodium dodecyl sulfate. The possible mechanism of photosensitization os characterized in terms of singlet oxygen efficiency of these dyes. Singlet oxygen quantum yields for bromine-substituted dyes are in the range of 0.3-0.5 depending on the solvent. For dye 1 no singlet oxygen prodn. is found. The photodynamic actions of these dyes in different cell lines are tested. It was found that dye 2 and dye 3 are efficient photosensitizers and mediate

eradication of K562, EM2, myeloid cell lines (CML) and the SMF-AI rhabdomyosarcoma line.

IT **62669-70-9P**, Rhodamine 123
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(phototoxicity of some bromine-substituted rhodamine dyes: synthesis, photophys. properties and application in leukemia photosensitizations with laser radiation)

L126 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:538169 CAPLUS
DOCUMENT NUMBER: 125:260967
TITLE: Spectroscopic and photophysical properties of some new rhodamine derivatives in cationic, anionic and neutral micelles
AUTHOR(S): Pal, P.; Zeng, H.; Durocher, G.; Girard, D.; Giasson, R.; Blanchard, L.; Gaboury, L.; Villeneuve, L.
CORPORATE SOURCE: Laboratoire de photophysique moleculaire, Departement de chimie, Universite de Montreal, C.P. 6128, Succ. Centre-ville, Montreal, Que., H3C 3J7, Can.
SOURCE: Journal of Photochemistry and Photobiology, A: Chemistry (1996), 98(1-2), 65-72
CODEN: JPPCEJ; ISSN: 1010-6030
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 10 Sep 1996
AB The spectroscopic and photophys. characterization of rhodamine 123 (dye 1), 4,5-dibromorhodamine Me ester (dye 2) and 4,5-dibromorhodamine Bu ester (dye 3) are reported in homogeneous media like water and some alcs. and also in microheterogeneous media; anionic sodium dodecylsulfate (SDS), cationic cetyltrimethylammonium bromide (CTAB) and neutral triton X-100 (TX) micelles. The selective biodistribution of these ionic drugs in tissues and membranes strongly influence their photosensitizing properties which have been part of our earlier studies. Results suggest that the hydrogen bonding capability of the amino end group lone pair of these dyes dominates in water. All these dyes interact with anionic SDS micelles. The interaction is mainly electrostatic in nature. At low SDS concns. (below c.m.c.), dye-SDS aggregate formation takes place. But above c.m.c. only the monomeric dye form is obsd. The penetration of dye 3 in SDS is a little less compared to dyes 1 and 2. Dyes 2 and 3 show a finite interaction with CTAB micelle unlike dye 1. With neutral TX micelles all the dyes form strong complexes. The fluorescence quantum yield (.PHI.F) of these three dyes in TX is lower. In time-resolved fluorescence expts., two lifetimes are obsd. The effects of the TX concn. on the fluorescence decay are measured. The decay assocd. spectra of dye 2 in TX are obtained by global compartmental anal. The dye-surfactant interaction mechanisms are also discussed.

IT **64-17-5**, Ethanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; spectroscopic and photophys. properties of rhodamine derivs. in homogeneous media and micelles)

IT **62669-70-9**, Rhodamine 123
RL: PRP (Properties)
(spectroscopic and photophys. properties of rhodamine derivs. in homogeneous media and micelles)

L126 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:642523 CAPLUS
DOCUMENT NUMBER: 117:242523
TITLE: Fluorescence properties and partitioning behavior of

esterified and unesterified rhodamines
AUTHOR(S): El Baraka, Mohamed; Deumie, Michel; Viallet, Pierre; Lampidis, Theodor J.
CORPORATE SOURCE: Lab. Chim. Phys., Univ. Perpignan, Perpignan, 66860, Fr.
SOURCE: Journal of Photochemistry and Photobiology, A: Chemistry (1991), 62(2), 195-216
CODEN: JPPCEJ; ISSN: 1010-6030
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 13 Dec 1992
AB The fluorescence characteristics of two esterified (RTME and R123) and two unesterified (R110 and RB) rhodamines were detd. in water as a function of pH, and their partitioning between water (W) and an org. solvent phase (OS) was detd. RTME and R123 exist in water as the esterified fluorescent form Re until Re is transformed via the zwitterionic R .+-. species into a non-fluorescent photoproduct RX in alk. pH. R110 and RB exist in water as cationic R + H, zwitterionic R .+-. and lactonic RO mol. structures, both Rc + H and R .+-. being fluorescent; all these species are in tenuous equil. depending on pH. The solute-solvent interactions change considerably upon excitation; RO and (R + H, R .+-.) are the predominant forms in the S0 and S1 states resp. The dyes are more and more partitioned into the OS phase of an OS-W mixt. as the size of their N-alkyl substitutes is increased. Two biphasic (1:1) systems were studied with OS being n-octanol, then cyclohexane. The largest dye RB is more trapped in the OS phases than the other dyes whatever the pH of the W phase is. When the W phase is at neutral pH, RB is almost totally trapped in octanol and its extn. percentage ERB = 0.97 is twice that of the other dyes. The partition coeffs. measured for R110, RB, RTME, R123 in octanol are resp. P = 0.8, 30, 1.2, 1.2; RB is again more partitioned in cyclohexane (ERB = 0.85) than R110 (ER110 = 0.07) when esterified dyes are insol.
IT **62669-70-9**
RL: USES (Uses)
(fluorescence properties and partitioning between water and org. solvent of, pH effect on)
IT **64-17-5**, Ethanol, properties
RL: PRP (Properties)
(solvent effect of, on fluorescence and partitioning behavior of esterified and unesterified rhodamines)

L126 ANSWER 5 OF 7 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002307348 EMBASE
TITLE: Considerations in the use of cerebrospinal fluid pharmacokinetics to predict brain target concentrations in the clinical setting: Implications of the barriers between blood and brain.
AUTHOR: De Lange E.C.M.; Danhof M.
CORPORATE SOURCE: Dr. E.C.M. De Lange, LACDR/Pharmacology, Sylvius Laboratories, PO Box 9503, Leiden 2300 RA, Netherlands. l.lange@lacdr.leidenuniv.nl
SOURCE: Clinical Pharmacokinetics, (2002) 41/10 (691-703).
Refs: 135
ISSN: 0312-5963 CODEN: CPKNDH
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In the clinical setting, drug concentrations in cerebrospinal fluid (CSF) are sometimes used as a surrogate for drug concentrations at the target

site within the brain. However, the brain consists of multiple compartments and many factors are involved in the transport of drugs from plasma into the brain and the distribution within the brain. In particular, active transport processes at the level of the blood-brain barrier and blood-CSF barrier, such as those mediated by P-glycoprotein, may lead to complex relationships between concentrations in plasma, ventricular and lumbar CSF, and other brain compartments. Therefore, CSF concentrations may be difficult to interpret and may have limited value. Pharmacokinetic data obtained by intracerebral microdialysis monitoring may be used instead, providing more valuable information. As non-invasive alternative techniques, positron emission tomography or magnetic resonance spectroscopy may be of added value.

L126 ANSWER 6 OF 7 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001422249 EMBASE
TITLE: Effect of endotoxin on P-glycoprotein-mediated biliary and renal excretion of rhodamine-123 in rats.
AUTHOR: Ando H.; Nishio Y.; Ito K.; Nakao A.; Wang L.; Ying Lan Zhao; Kitaichi K.; Takagi K.; Hasegawa T.
CORPORATE SOURCE: T. Hasegawa, Department of Medical Technology, Nagoya Univ. School of Hlth. Sci., 1-1-20 Daikominami, Higashi-ku, Nagoya 461-8673, Japan. hasegawa@met.nagoya-u.ac.jp
SOURCE: Antimicrobial Agents and Chemotherapy, (2001) 45/12 (3462-3467).
Refs: 43
ISSN: 0066-4804 CODEN: AMACCQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The effects of Klebsiella pneumoniae endotoxin on the biliary excretion and renal handling of rhodamine-123 were investigated in rats at different times after intraperitoneal injection (1 mg/kg of body weight). The typical substrates for P glycoprotein, i.e., cyclosporine, colchicine, and erythromycin, inhibited the biliary clearance of rhodamine-123, whereas a substrate for organic cation transporter, cimetidine, did not inhibit clearance, suggesting that rhodamine-123 is transported mainly by P glycoprotein. The biliary, renal, and tubular secretory clearances of rhodamine-123 and the glomerular filtration rate significantly decreased 6 h after injection of endotoxin but returned to control levels by 24 h. These results suggest that endotoxin-induced decreases in P-glycoprotein-mediated biliary excretion and renal handling of rhodamine-123 were probably due to impairment of P-glycoprotein-mediated transport ability. Pretreatment with pentoxifylline (50 mg/kg) significantly inhibited endotoxin-induced increases in tumor necrosis factor alpha (TNF-a) levels in plasma, which ameliorated the endotoxin-induced reduction of the biliary excretion of rhodamine-123. It is likely that endotoxin-induced impairment of the transport of rhodamine-123 is caused, in part, by overproduction of TNF-.alpha.. The effect of endotoxin on the expression of P-glycoprotein mRNA in liver and kidneys of rats was investigated by using a reverse transcriptase PCR. The expression of Mdr1a mRNA in both liver and kidney decreased 6 h after endotoxin injection and returned to control levels after 24 h, whereas the expression of Mdr1b mRNA in liver increased at both times and that in kidney decreased at 24 h. These findings suggest that K. pneumoniae endotoxin dramatically decreases P-glycoprotein-mediated biliary and renal excretion of rhodamine-123 probably by decreasing the expression of Mdr1a, which is likely due to increased plasma TNF-.alpha. levels.

L126 ANSWER 7 OF 7 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2001047621 EMBASE

TITLE: Pharmacokinetic interaction of cytochrome P450 3A-related compounds with rhodamine 123, a P-glycoprotein substrate, in rats pretreated with dexamethasone.

AUTHOR: Yumoto R.; Murakami T.; Sanemasa M.; Nasu R.; Nagai J.; Takano M.

CORPORATE SOURCE: Dr. M. Takano, Institute of Pharmaceutical Sciences, Faculty of Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. takanom@pharm.hiroshima-u.ac.jp

SOURCE: Drug Metabolism and Disposition, (2001) 29/2 (145-151). Refs: 53
ISSN: 0090-9556 CODEN: DMDSAI

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The effect of pretreatment with dexamethasone (DEX) on drug-drug interactions between rhodamine 123 (Rho123), a P-glycoprorein (P-gp) substrate, and midazolam, a cytochrome P450 (CYP) 3A substrate, or verapamil, a P-gp/CYP3A substrate, was studied in rats. Rats were pretreated with DEX (100 mg/kg/day, oral) for 2 days. Western blot analysis with a monoclonal antibody for P-gp, C219, revealed that DEX pretreatment increased P-gp level in the intestine 1.9-fold, but not in the liver. In vitro metabolism study of erythromycin in microsomal suspensions indicated the 9.7-fold increase of CYP3A activity in the liver, but not in the intestine, by DEX pretreatment, in an in vivo study, DEX pretreatment increased P-gp-mediated exsorption clearance of Rho123 from blood to the intestinal lumen approximately 2-fold, but not biliary clearances, in good agreement with the results of Western blot analysis. In untreated rats, midazolam (100 .mu.M) or verapamil (30 or 100 .mu.M) added in the intestinal perfusate (single perfusion) decreased the exsorption clearance and biliary clearance of Rho123 by approximately 30 to 50%. in DEX-pretreated rats, however, the inhibitory potency of midazolam in the liver significantly decreased compared with that in untreated rats, although the potency in the intestine did not change. The inhibitory potency of verapamil decreased both in the intestine and liver by DEX pretreatment. In conclusion, it was demonstrated that DEX pretreatment affects not only P-gp-mediated disposition of Rho123 but also pharmacokinetic interactions of P-gp/CYP3A-related compounds with Rho123, probably because concentrations of substrates/inhibitors at target sites such as the intestine and liver are varied.

```
=> fil capl; d que 130
FILE 'CAPLUS' ENTERED AT 14:30:01 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 27 Feb 2004  VOL 140 ISS 10
FILE LAST UPDATED: 26 Feb 2004  (20040226/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L5            1 SEA FILE=REGISTRY ABB=ON  ETHANOL/CN
L7       166693 SEA FILE=CAPLUS ABB=ON  L5
L10           1 SEA FILE=REGISTRY ABB=ON  DEXTROSE/CN
L11           2 SEA FILE=REGISTRY ABB=ON  GLUCOSE/CN
L12           1 SEA FILE=REGISTRY ABB=ON  SUCROSE/CN
L14      211106 SEA FILE=CAPLUS ABB=ON  (L10 OR L11 OR L12)
L20      143470 SEA FILE=CAPLUS ABB=ON  DRUG DELIVERY SYSTEMS+OLD/CT
L22      159411 SEA FILE=CAPLUS ABB=ON  INTRAVENOUS?/OBI OR IV/OBI OR I V/OBI
L24       13235 SEA FILE=CAPLUS ABB=ON  L14(L)(THU OR BAC OR PAC OR PKT OR
                DMA)/RL
L25        6773 SEA FILE=CAPLUS ABB=ON  L7(L)(THU OR BAC OR PAC OR PKT OR
                DMA)/RL
L30           6 SEA FILE=CAPLUS ABB=ON  L24 AND L25 AND L22 AND L20


=> s l30 not (l8 or l18 or l3)

L127          6 L30 NOT (L8 OR L18 OR L3)

=> fil medl; d que l75; d que l80

FILE 'MEDLINE' ENTERED AT 14:30:02 ON 27 FEB 2004

 FILE LAST UPDATED: 25 FEB 2004 (20040225/UP).  FILE COVERS 1958 TO DATE.

 On December 14, 2003, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description
 on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
```

previously printed

\ Roles
THU - therapeutic use
BAC - Biological activity
PAC - pharmacologic activity
PKT - pharmacokinetics
DMA - drug mechanism of action

```
L61        47184 SEA FILE=MEDLINE ABB=ON  ETHANOL/CT
L65        86952 SEA FILE=MEDLINE ABB=ON  GLUCOSE/CT
L66         1520 SEA FILE=MEDLINE ABB=ON  L65 AND L61
L70         7572 SEA FILE=MEDLINE ABB=ON  PHARMACEUTICAL SOLUTIONS+NT/CT
L75            0 SEA FILE=MEDLINE ABB=ON  L66 AND L70



L61        47184 SEA FILE=MEDLINE ABB=ON  ETHANOL/CT
L65        86952 SEA FILE=MEDLINE ABB=ON  GLUCOSE/CT
L71        30398 SEA FILE=MEDLINE ABB=ON  INFUSIONS, INTRAVENOUS/CT
L77        68616 SEA FILE=MEDLINE ABB=ON  ALCOHOL DRINKING/CT OR ALCOHOLISM/CT
L78         7254 SEA FILE=MEDLINE ABB=ON  ALCOHOLIC INTOXICATION/CT
L79           30 SEA FILE=MEDLINE ABB=ON  ALCOHOLIC NEUROPATHY/CT
L80            7 SEA FILE=MEDLINE ABB=ON  L71 AND L61 AND L65 NOT (L77 OR L78
                  OR L79)


=> s l80 not l59

L128           7 L80 NOT L59

=> fil embase; d que l104

FILE 'EMBASE' ENTERED AT 14:30:04 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

 FILE COVERS 1974 TO 26 Feb 2004 (20040226/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L99        80315 SEA FILE=EMBASE ABB=ON  ALCOHOL/CT
L100       87564 SEA FILE=EMBASE ABB=ON  GLUCOSE/CT
L103         969 SEA FILE=EMBASE ABB=ON  DRUG SOLUTION/CT
L104           3 SEA FILE=EMBASE ABB=ON  L99 AND L100 AND L103


=> s l104 not (192-193)

L129           3 L104 NOT ((L92 OR L93))

=> dup rem l128,l127,l129
FILE 'MEDLINE' ENTERED AT 14:30:32 ON 27 FEB 2004

FILE 'CAPLUS' ENTERED AT 14:30:32 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 14:30:32 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.
PROCESSING COMPLETED FOR L128
PROCESSING COMPLETED FOR L127
PROCESSING COMPLETED FOR L129
L130          16 DUP REM L128 L127 L129 (0 DUPLICATES REMOVED)
                 ANSWERS '1-7' FROM FILE MEDLINE
                 ANSWERS '8-13' FROM FILE CAPLUS
                 ANSWERS '14-16' FROM FILE EMBASE
```

=> d ibib ed ab hitrn 1-16

L130 ANSWER 1 OF 16 MEDLINE on STN
ACCESSION NUMBER: 96032481 MEDLINE
DOCUMENT NUMBER: 96032481 PubMed ID: 7573446
TITLE: Effects of ethanol, xylose, and glucose on canine jejunal motility.
AUTHOR: Charles F; Phillips S F
CORPORATE SOURCE: Gastroenterology Research Unit, Mayo Clinic, Rochester, Minnesota 55905, USA.
CONTRACT NUMBER: DK-32121 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1995 Sep) 269 (3 Pt 1) G363-9.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19980206
Entered Medline: 19951106
ED Entered STN: 19951227
Last Updated on STN: 19980206
Entered Medline: 19951106
AB Ethanol is an important source of calories that can cause certain gastrointestinal symptoms, notably diarrhea. To examine the effects of ethanol on the small bowel, we intraluminally perfused the jejunum of four dogs with ethanol (18, 9, 4.5, and 1.5%, wt/vol), D-xylose (30, 15, 7.5, and 4.5%, wt/vol), or glucose (30 and 5%, wt/vol). In other experiments, these solutes were infused intravenously. Saline was always given by the alternate route; jejunal manometry was recorded during and after the infusions. Phase III of the interdigestive cycle was delayed by all intraluminal infusions except for 4.5 and 1.5% ethanol, 4.5% xylose, and 5% glucose. In addition, the onset of irregular contractile activity was delayed more with intraluminal ethanol than with intraluminal xylose or intraluminal glucose ($P < 0.01$). When administered intraluminally, ethanol and xylose appeared in blood but only ethanol equilibrated fully between the lumen and blood. Intravenous infusions of ethanol and xylose, but not glucose, also delayed the return of phase III. When given intravenously, ethanol and xylose were recovered from the lumen, whereas glucose never was. Ethanol and xylose had comparable effects on the canine small bowel; they induced prolonged periods of irregular contractile activity and delayed the return of phase III. These effects were seen rapidly when solutes were administered intraluminally and more slowly when they were given intravenously. These results suggest that local luminal mechanisms stimulated by solutes influence small bowel motility, and they imply that the gut recognizes solutes whether or not these molecules are metabolizable.

L130 ANSWER 2 OF 16 MEDLINE on STN
ACCESSION NUMBER: 95028522 MEDLINE
DOCUMENT NUMBER: 95028522 PubMed ID: 7942061
TITLE: Microdialysis of rat skeletal muscle and adipose tissue: dynamics of the interstitial glucose pool.
AUTHOR: Fuchi T; Rosdahl H; Hickner R C; Ungerstedt U; Henricksson J
CORPORATE SOURCE: Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden.
SOURCE: ACTA PHYSIOLOGICA SCANDINAVICA, (1994 Jun) 151 (2) 249-60.
Journal code: 0370362. ISSN: 0001-6772.
PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19980206
Entered Medline: 19941117
ED Entered STN: 19941222
Last Updated on STN: 19980206
Entered Medline: 19941117
AB Microdialysis was evaluated as a method for studying glucose metabolism in skeletal muscle. Dialysis probes (0.5 x 10 mm) were perfused at 0.5 or 1.0 microliter min-1. Based upon perfusion with glucose, the muscle interstitial glucose concentration was estimated to be 6.9 +/- 0.3 mM (n = 14), which was not significantly different from the blood glucose level. With insulin infusion (1200 mU kg-1 body wt i.v.), the insulin-induced change in the glucose concentration of the interstitial space of muscle was of equal magnitude to that of blood and adipose tissue. In spite of this, when the perfusion medium was not supplemented with glucose, the glucose concentration decreased more in skeletal muscle dialysates (to 36.7 +/- 4.9% of the initial level) than in blood (to 29.7 +/- 5.0%) but less than in adipose tissue (to 17.7 +/- 4.9% of the initial level) ($P < 0.05$). The results indicate that these differences are due to tissue-specific differences in the dynamic balance between the supply to, and removal from, the interstitial glucose pool. This balance is revealed as a result of the constant glucose drainage by the microdialysis probe. The present results show that, in skeletal muscle, increases in glucose uptake occur with a concomitant increase in tissue blood flow as revealed by the microdialysis ethanol technique, whereas in adipose tissue the glucose uptake increases in the absence of a corresponding increase in blood flow.

L130 ANSWER 3 OF 16 MEDLINE on STN
ACCESSION NUMBER: 93131080 MEDLINE
DOCUMENT NUMBER: 93131080 PubMed ID: 8420819
TITLE: Effects of ethanol on carbohydrate metabolism in the elderly.
AUTHOR: Boden G; Chen X; Desantis R; White J; Mozzoli M
CORPORATE SOURCE: Division of Endocrinology/Metabolism, Temple University School of Medicine, Philadelphia, PA.
CONTRACT NUMBER: R01-AG-07988 (NIA)
RR-349 (NCRR)
T32-DK-07162 (NIDDK)
SOURCE: DIABETES, (1993 Jan) 42 (1) 28-34.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930226
Last Updated on STN: 19980206
Entered Medline: 19930212
ED Entered STN: 19930226
Last Updated on STN: 19980206
Entered Medline: 19930212
AB We have previously reported that in young men, ethanol caused acute insulin resistance, but compensatory insulin secretion prevented deterioration of glucose tolerance (1). In this study, we tested the hypothesis that elderly men, because of their pre-existing insulin resistance and compromised insulin secretory capacity, may experience worsening of their glucose tolerance after ethanol. Nine elderly men (65.7 +/- 0.8 yr, BMI 25.8 +/- 1.4 kg/m2) received ethanol (13 mmol/kg for

30 min i.v.) or saline followed 30 min later by i.v. glucose (2.8 mmol/kg for 5 min). To determine the mechanism of the ethanol effect, six of the men underwent euglycemic-hyperinsulinemic (approximately 350 pM) clamping with simultaneous infusion of ethanol or saline. Muscle biopsies were obtained before and 1 and 4 h after insulin infusion. In all nine men, glucose concentrations after i.v. glucose were higher after ethanol than after saline, whereas insulin was the same and glucose tolerance decreased by 23% (Kg 2.41 +/- 0.2 vs. 1.86 +/- 0.1%/min, P < 0.01). Ethanol reduced insulin-stimulated glucose uptake from 40.6 +/- 3.1 to 25.6 +/- 1.9 mumol.kg-1.min-1 (-37%, P < 0.05), glucose oxidation from 11.7 +/- 1.1 to 7.0 +/- 0.7 mumol.kg-1.min-1 (-33%, P < 0.01), and glucose storage from 28.7 +/- 2.4 to 18.6 +/- 1.7 mumol.kg-1.min-1 (-35%, P < 0.01). Ethanol increased muscle lactate concentration from 0.49 +/- 0.14 to 1.99 +/- 0.99 mumol/mg protein (P < 0.05), but had no effects on muscle concentration of free glucose, G-6-P, and citrate concentrations, nor did it affect muscle GS activity.(ABSTRACT TRUNCATED AT 250 WORDS)

L130 ANSWER 4 OF 16 MEDLINE on STN
ACCESSION NUMBER: 89285400 MEDLINE
DOCUMENT NUMBER: 89285400 PubMed ID: 2660591
TITLE: Contributions of gluconeogenesis and glycogenolysis during glucose counterregulation in normal humans.
AUTHOR: Lecavalier L; Bolli G; Cryer P; Gerich J
CORPORATE SOURCE: Endocrine Research Unit, Mayo Medical School, Rochester, Minnesota 55905.
CONTRACT NUMBER: DK-20411 (NIDDK)
DK-20479 (NIDDK)
DK-27085 (NIDDK)
+
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1989 Jun) 256 (6 Pt 1) E844-51.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19980206
Entered Medline: 19890718
ED Entered STN: 19900309
Last Updated on STN: 19980206
Entered Medline: 19890718
AB To estimate the relative contributions of gluconeogenesis and glycogenolysis to the increase in hepatic glucose output (HGO) during glucose counterregulation under conditions simulating clinical insulin hypoglycemia, we induced moderate hypoglycemia (approximately 55 mg/dl) with a continuous infusion of insulin that resulted in physiological hyperinsulinemia (approximately 20 microU/ml) in eight normal volunteers and estimated gluconeogenesis by two methods: an isotopic approach in which appearance of plasma glucose derived from lactate was determined and another approach in which we infused alcohol along with insulin to block gluconeogenesis and used the exogenous glucose required to prevent greater hypoglycemia as an index of gluconeogenesis. Both methods gave similar results. Initially glycogenolysis accounted for approximately 85% of HGO; however, once hypoglycemia became established, the contribution of gluconeogenesis increased progressively to 77 +/- 10 (isotopic method) and 94 +/- 10% (alcohol method) of overall HGO. We conclude that in normal humans during moderate protracted hypoglycemia induced by physiological hyperinsulinemia, gluconeogenesis is the predominant factor responsible for the counterregulatory increase in HGO and that increased gluconeogenesis rather than increased glycogenolysis is the primary mechanism preventing development of greater hypoglycemia.

L130 ANSWER 5 OF 16 MEDLINE on STN
ACCESSION NUMBER: 89149876 MEDLINE
DOCUMENT NUMBER: 89149876 PubMed ID: 3067730
TITLE: Effect of oral glucose on the rate of metabolism of ethanol in humans.
AUTHOR: Mascord D; Smith J; Starmer G A; Whitfield J B
CORPORATE SOURCE: Department of Pharmacology, University of Sydney, NSW, Australia.
SOURCE: ALCOHOL AND ALCOHOLISM, (1988) 23 (5) 365-70.
Journal code: 8310684. ISSN: 0735-0414.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198904
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19980206
Entered Medline: 19890414
ED Entered STN: 19900306
Last Updated on STN: 19980206
Entered Medline: 19890414
AB We have tested whether the effect of carbohydrate on the rate of alcohol metabolism can be reproduced by glucose alone. Ten male subjects were given ethanol by intravenous infusion until a steady state was established and 100 g glucose in solution was then taken orally. The rate of alcohol metabolism, measured as the rate of infusion required to maintain a constant breath alcohol reading, increased significantly after glucose but there were differences between the subjects. The presence or absence of a change in the rate of alcohol metabolism after glucose was associated with the subject's fasting rate and with their glucose tolerance.

L130 ANSWER 6 OF 16 MEDLINE on STN
ACCESSION NUMBER: 89170238 MEDLINE
DOCUMENT NUMBER: 89170238 PubMed ID: 3148453
TITLE: Effect of alcohol and glucose infusion on pituitary-gonadal hormones in normal females.
AUTHOR: Becker U; Gluud C; Bennett P; Micic S; Svenstrup B; Winkler K; Christensen N J; Hardt F
CORPORATE SOURCE: Medical Department, Hvidovre University Hospital, Denmark.
SOURCE: DRUG AND ALCOHOL DEPENDENCE, (1988 Oct) 22 (1-2) 141-9.
Journal code: 7513587. ISSN: 0376-8716.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198904
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19980206
Entered Medline: 19890428
ED Entered STN: 19900306
Last Updated on STN: 19980206
Entered Medline: 19890428
AB During 1 h, median 976 mmol ethanol in 5.5% glucose was administered i.v. to six healthy female volunteers (aged 26-37 years) in the luteal phase of the menstrual cycle. The median maximal blood ethanol concentration was median 33.5 mmol/l and serum ethanol concentrations of 2 mmol/l were reached after 8 h. Four of the women participated in a control experiment with infusion of an equal volume of glucose 5.5%. Venous blood samples were drawn 5 times during the 24-h follow up period. Serum concentrations of sex steroids and pituitary hormones decreased in both ethanol and control experiments and the results did not differ significantly. The lowest hormone concentrations were observed 1-5 h after the start of

infusion. Oestradiol, oestrone and oestrone-sulphate concentrations decreased 24-46% compared to basal values. 5 alpha-dihydro-testosterone levels decreased 23-31%, androstenedione and dehydroepiandrosterone-sulphate levels decreased 6-48%, while testosterone levels did not change significantly. Prolactin concentrations were reduced by 41-51% of basal values and luteinizing hormone concentrations by 37-68% Follicle stimulating hormone levels did not change significantly. Stress factors or haemodilution are not likely explanations of the observed changes in hormone concentrations. A circadian rhythm could not explain changes in hormones of non-adrenal origin.

L130 ANSWER 7 OF 16 MEDLINE on STN
ACCESSION NUMBER: 88269052 MEDLINE
DOCUMENT NUMBER: 88269052 PubMed ID: 3291882
TITLE: Alcohol decreases insulin sensitivity in healthy subjects.
AUTHOR: Shah J H
CORPORATE SOURCE: Department of Medicine, Harry S. Truman Memorial Veterans Hospital, Columbia, MO 65201.
SOURCE: ALCOHOL AND ALCOHOLISM, (1988) 23 (2) 103-9.
Journal code: 8310684. ISSN: 0735-0414.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198808
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19980206
Entered Medline: 19880824
ED Entered STN: 19900308
Last Updated on STN: 19980206
Entered Medline: 19880824
AB To study the effect of alcohol on glucose and insulin metabolism, a simultaneous infusion of glucose and insulin was given for 150 min to healthy volunteers, once during alcohol and once during calorie-free gingerale (control) ingestion. During alcohol intake, the average steady-state (between 100 and 150 min) glucose of 5.44 +/- 0.39 mmol/l. and the average steady-state insulin of 6.3 +/- 1.1 ng/ml were significantly higher than those (4.0 +/- 0.39 mmol/l. of glucose and 4.4 +/- 0.6 ng/ml of insulin) observed during the control state. Despite the higher steady-state insulin concentrations, the glucose metabolism was significantly less during alcohol ingestion. These findings suggest alcohol-induced impairment in glucose metabolism is caused by a decreased tissue sensitivity to insulin.

L130 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:1006706 CAPLUS
DOCUMENT NUMBER: 140:31522
TITLE: Antifungal parenteral composition of echinocandin
INVENTOR(S): Stogniew, Martin
PATENT ASSIGNEE(S): Vicuron Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003105767	A2	20031224	WO 2003-US18754	20030612

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-172678 A 20020613

ED Entered STN: 26 Dec 2003

AB Parenteral pharmaceutical formulations contg. an echinocandin antifungal compd. and an aq. solvent are provided, comprising ethanol, for example about 20% wt./vol. ethanol. The parenteral pharmaceutical formulation may further include one or more additives, such as a stabilizing agent, buffer or tonicity agent. The parenteral pharmaceutical formulations are useful in extending the shelf life and improving the soly. of the echinocandin antifungal compd. For example, to a pH 4.5 buffer soln. contg. 25 g polysorbate 80 and 1.1 g of tartaric acid, 10 g anidulafungin in water for injection forming slurry was added and the liq. was mixed until all the slurried drug was dissolved. The fructose (10 g) and mannitol (50 g) were added and mixed until dissolved. Addnl. water for injection was added to bring the soln. to final vol. and pH was adjusted, if necessary, to pH 4.5. The soln. was sterilized by membrane filtration. Aliquots (3.5 mL) of the sterile filtered bulk soln. were filled into the sterile glass vials and lyophilized. The lyophilized product was reconstituted a two step process. In the first step, the solid formulation contg. 35 mg anidulafungin, and optionally other components of the formulation, was reconstituted in a 10 mL soln. of 20% wt./vol. ethanol in water for injection. This mixt. was then dild. 7 fold in a soln. of 5% dextrose in sterile water to obtain an i.v. injection soln.

IT **57-50-1**, Sucrose, biological studies **64-17-5**, Ethanol, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prepn. of antifungal parenteral soln. of echinocandin)

L130 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:251851 CAPLUS
DOCUMENT NUMBER: 136:284442
TITLE: Formulations of paclitaxel and its derivatives or analogs entrapped into nanoparticles of polymeric micelles
INVENTOR(S): Burman, Anand C.; Mukherjee, Rama; Khattar, Dhiraj; Kumar, Mukesh; Bala, Honey; Shrivastava, Rajiv Kumar
PATENT ASSIGNEE(S): Dabur Research Foundation, India
SOURCE: U.S., 8 pp., Cont.-in-part of U.S. Ser. No. 401,927.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6365191	B1	20020402	US 2000-667417	20000921
US 6322817	B1	20011127	US 1999-401927	19990923

PRIORITY APPLN. INFO.: IN 1999-DE263 A 19990217
US 1999-401927 A2 19990923
IN 2000-DE641 A 20000711

ED Entered STN: 04 Apr 2002

AB This invention relates to pharmaceutical formulations of paclitaxel, its derivs. or analogs entrapped into nanoparticles of copolymeric micelles, a process for prepg. the same and the use thereof. For example, the polymer (5 mg) was dissolved in 5 mL of the dilg. fluid followed by the addn. of

the anionic surfactant sodium deoxycholate (5 mg) to obtain a clear soln. Paclitaxel soln. in abs. alc. (20 mg/mL) was then added to the soln. of polymer and the surfactant to obtain drug concns. of 0.1, 0.15 and 0.2 mg/mL. Different dilg. fluids were tried and the stability of the resulting drug solns. are tabulated. Dextrose had a stabilizing effect on the drug soly. as reflected in the stability of the drug soln.

IT **50-99-7**, Dextrose, biological studies **64-17-5**, Ethanol, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(polymeric micelle nanoparticles for **i.v.** formulations of paclitaxel and its derivs. or analogs for treatment of proliferative diseases)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L130 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:903792 CAPLUS
DOCUMENT NUMBER: 136:42838
TITLE: Delivery systems for a peptide, protein or nucleic acid
INVENTOR(S): Barman, Shikha P.; McKeever, Una; Hedley, Mary Lynne
PATENT ASSIGNEE(S): Zycos Inc., USA
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001093835	A1	20011213	WO 2001-US17971	20010601
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1292285	A1	20030319	EP 2001-946064	20010601
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003535122	T2	20031125	JP 2002-501408	20010601
PRIORITY APPLN. INFO.:			US 2000-208830P P	20000602
			WO 2001-US17971 W	20010601

ED Entered STN: 14 Dec 2001
AB The invention features a microparticle compn. for the delivery of bioactive agents into cells that includes a polymeric matrix, an anionic or zwitterionic lipid having a pKa of < .apprx. 2.5, and a bioactive agent, e.g. a peptide, protein, or nucleic acid. The compns. of the invention can be used to deliver bioactive compds., such as nucleic acids encoding immunostimulatory peptides and/or therapeutic proteins. For example, poly(glycolic acid-lactic acid) microparticles contg. DNA encoding a peptide having an amino acid sequence of proteolipid protein (PLP) were prepd. and injected i.v. to a multiple sclerosis patient whose T cells secrete excess Th1 cytokines (i.e., IL-2 and .gamma.-IFN). Expression of PLP-like peptide by APCs results in the switching of the cytokine profile of the T cells, such that they instead produce Th2 cytokines (i.e., IL-4 and IL-10) in response to autoantigens. Also, DNA encapsulated in PEG-DSPE contg. microparticles was protected from the nuclease, compared to DNA in non-lipid contg. microparticles.

IT **64-17-5**, Ethanol, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(DNA pptn. by; microparticles for delivery of peptide, protein or nucleic acid)
IT **57-50-1**, Sucrose, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(microparticles for delivery of peptide, protein or nucleic acid)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L130 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:911288 CAPLUS
DOCUMENT NUMBER: 134:70420
TITLE: Rufomycin derivatives useful as antibiotics
INVENTOR(S): Kulanthaivel, Palaniappan; Vasudevan, Venkatraghavan
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078797	A1	20001228	WO 2000-US15038	20000615

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-140072P P 19990621
OTHER SOURCE(S): MARPAT 134:70420
ED Entered STN: 29 Dec 2000
AB The present invention provides rufomycin factors and derivs. and pharmaceutical formulations, which are useful as antimicrobials esp. as antimycobacterials. Thus, Streptomyces macrosporeus (DSM-12818) was cultivated in fermentors as large as 5000 L for 90-170 h at 30 .degree.C in an optimized industrial medium contg. cottonseed flour, cane molasses, glycerol, glucose, potato dextrin, phytic acid and salts. The harvested fermn. broth was mixed with acetone, centrifuged, and the supernatant was filtered. Rufomycin factors were obtained by ion exchange chromatog. of the filtered acetone ext. The isolated rufomycin factors then served as backbones for the chem. synthesis of 163 rufomycin derivs. Several of the rufomycin factors and derivs. showed antimycobacterial activity against Mycobacterium tuberculosis. Also presented are pharmaceutical formulations for the delivery of rufomycin factors and derivs. as capsules, suspensions, i.v. solns., or topical creams.
IT **50-99-7**, Dextrose, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(rufomycin derivs. useful as antibiotics)
IT **64-17-5**, Ethanol, biological studies
RL: PEP (Physical, engineering or chemical process); RCT (Reactant); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(rufomycin derivs. useful as antibiotics)
IT **57-50-1**, Sucrose, biological studies

RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(rufomycin derivs. useful as antibiotics)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L130 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:911286 CAPLUS
DOCUMENT NUMBER: 134:70419
TITLE: Rufomycins and derivatives useful as inhibitors of multi-drug resistance associated protein-1 (MRP-1)
INVENTOR(S): Kulanthaivel, Palaniappan; Vasudevan, Venkatraghavan
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078795	A2	20001228	WO 2000-US15020	20000608
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1192178	A2	20020403	EP 2000-946770	20000608
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-140362P P 19990621
WO 2000-US15020 W 20000608
OTHER SOURCE(S): MARPAT 134:70419
ED Entered STN: 29 Dec 2000
AB The present invention provides rufomycin factors and derivs. and pharmaceutical formulations, which are useful as in combination with other chemotherapeutic agents for inhibiting multi-drug resistance. Thus, these compds. enhance the the efficacy of other agents that are subject to multi-drug resistance esp. with those agents used in treating malaria and cancer. Streptomyces macrosporeus (DSM-12818) was cultivated in fermentors as large as 5000 L for 90-170 h at 30 .degree.C in an optimized industrial medium contg. cottonseed flour, cane molasses, glycerol, glucose, potato dextrin, phytic acid and salts. The harvested fermn. broth was mixed with acetone, centrifuged, and the supernatant was filtered. Rufomycin factors were obtained by ion exchange chromatog. of the filtered acetone ext. The isolated rufomycin factors then served as backbones for the chem. synthesis of 163 rufomycin derivs. Several of the rufomycin factors and derivs. were able to enhance the efficacy of the anticancer drugs vincristine, doxorubicin and etoposide against the resistant cell lines HL60ADR, HL60VCR and HeLaT5. Also presented are pharmaceutical formulations for the delivery of rufomycin factors and derivs. as capsules, suspensions, i.v. solns., or topical creams.
IT **50-99-7**, Dextrose, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(rufomycins and derivs. useful as inhibitors of multi-drug resistance assocd. protein-1 (MRP-1))
IT **64-17-5**, Ethanol, biological studies

RL: PEP (Physical, engineering or chemical process); RCT (Reactant); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(rufomycins and derivs. useful as inhibitors of multi-drug resistance assocd. protein-1 (MRP-1))

IT **57-50-1**, Sucrose, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(rufomycins and derivs. useful as inhibitors of multi-drug resistance assocd. protein-1 (MRP-1))

L130 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:861473 CAPLUS
DOCUMENT NUMBER: 134:32972
TITLE: Porous drug matrixes containing polymers and sugars and methods of their manufacture
INVENTOR(S): Straub, Julie; Bernstein, Howard; Chickering, Donald E., III; Khatak, Sarwat; Randall, Greg
PATENT ASSIGNEE(S): Acusphere, Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072827	A2	20001207	WO 2000-US14578	20000525
WO 2000072827	A3	20010125		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6395300	B1	20020528	US 1999-433486	19991104
EP 1180020	A2	20020220	EP 2000-939365	20000525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010984	A	20020430	BR 2000-10984	20000525
JP 2003500438	T2	20030107	JP 2000-620939	20000525
NZ 516083	A	20030829	NZ 2000-516083	20000525
AU 768022	B2	20031127	AU 2000-54459	20000525
US 2002041896	A1	20020411	US 2001-798824	20010302
US 6610317	B2	20030826		
NO 2001005753	A	20020128	NO 2001-5753	20011126
ZA 2001010347	A	20030730	ZA 2001-10347	20011218

PRIORITY APPLN. INFO.:

US 1999-136323P	P	19990527
US 1999-158659P	P	19991008
US 1999-433486	A	19991104
US 2000-186310P	P	20000302
WO 2000-US14578	W	20000525

ED Entered STN: 08 Dec 2000
AB Drugs, esp. low aq. soly. drugs, are provided in a porous matrix form, preferably microparticles, which enhances dissoln. of the drug in aq. media. The drug matrixes preferably are made using a process that includes (i) dissolving a drug, preferably a drug having low aq. soly., in a volatile solvent to form a drug soln., (ii) combining at least one pore forming agent with the drug soln. to form an emulsion, suspension, or second solns., and (iii) removing the volatile solvent and pore forming

agent from the emulsion, suspension, or second soln. to yield the porous matrix of drug. The pore forming agent can be either a volatile liq. that is immiscible with the drug solvent or a volatile solid compd., preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissoln. following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aq. medium and administered parenterally, or processed using std. techniques into tablets or capsules for oral administration. Paclitaxel or docetaxel can be provided in a porous matrix form, which allows the drug to be formulated without solubilizing agents and administered as a bolus. For example, a nifedipine-loaded org. soln. was prepd. by dissolving 9.09 g of PEG 3350, 2.27 g of nifedipine, and 0.009 g of lecithin in 182 mL of methylene chloride. An aq. soln. was prepd. by dissolving 3.27 g of NH4HCO3 and 0.91 g of PEG 3350 in 1.82 mL of water. The aq. and org. solns. were homogenized and resulting emulsion was spray dried. A suspension of the porous nifedipine drug matrix was prepd. in 5% dextrose soln. at a concn. of 2.5 mg/mL. A bolus injection of the suspension was tolerated when administrated to dogs.

IT **50-99-7**, Dextrose, biological studies
RL: PEP (Physical, engineering or chemical process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(prepn. of porous matrixes contg. hydrophilic polymers and sugars for enhancement of drug dissoln.)

IT **64-17-5**, Ethanol, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prepn. of porous matrixes contg. hydrophilic polymers and sugars for enhancement of drug dissoln.)

L130 ANSWER 14 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001109784 EMBASE

TITLE: DAMGO, a .mu.-opioid agonist and cholecystokinin-octapeptide have dual modulatory effects on capsaicin-activated current in rat dorsal root ganglion neurons.

AUTHOR: Eun S.-Y.; Kim J.; Lee J.; Jung S.J.; Park J.M.; Park Y.K.; Kim D.; Kim S.J.; Kwak J.; Kim J.

CORPORATE SOURCE: J. Kim, Department of Physiology/Biophysics, Seoul Natl. Univ. College of Med., 28 Yongon-dong, Chongno-gu, Seoul 110-799, Korea, Republic of. Kimjun@plaza.snu.ac.kr

SOURCE: Korean Journal of Physiology and Pharmacology, (2001) 5/1 (71-78).
Refs: 23
ISSN: 1226-4512 CODEN: KJPPFS

COUNTRY: Korea, Republic of

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
052 Toxicology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Capsaicin, a pungent ingredient of hot pepper, elicits an intense burning pain when applied cutaneously and intradermally. Activation of capsaicin-gated channel in C-type dorsal root ganglion (DRG) neurons produces nonselective cationic currents. Although electrophysiological and biochemical properties of capsaicin-activated current (I(CAP)) were studied, the regulatory mechanism and intracellular signaling pathway are still unclear. In the present study, we investigated the modulations of I(CAP) by DAMGO (.mu.-opioid agonist) and cholecystokinin octapeptide

(CCK-8). In 18 out of 86 cells, the amplitude of I(CAP) was significantly increased by DAMGO and completely reversed after washout, while I(CAP) was decreased by DAMGO in 25 cells. In 43 cells, DAMGO had no effect on I(CAP). Mean action potential duration was significantly different between 'increased-by-DAMGO' group and 'decreased-by-DAMGO' group. Mean amplitudes of I(H) were not significantly different between both groups. CCK-8 reversibly enhanced the amplitude of I(CAP) (5/13). DAMGO also increased I(CAP) amplitude significantly in the same cells. The amplitude of I(CAP) was increased in additive manner by combined applications of DAMGO and CCK-8 in these cells. These results suggest that DAMGO and CCK-8 can either increase or decrease I(CAP) presumably depending on the subtypes of DRG cells and classified by electrophysiological properties.

L130 ANSWER 15 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 95354571 EMBASE
DOCUMENT NUMBER: 1995354571
TITLE: Stability of the i.v. and oral formulations of etoposide in solution.
AUTHOR: Joel S.P.; Clark P.I.; Slevin M.L.
CORPORATE SOURCE: Department of Medical Oncology, St. Bartholomew's Hospital,West Smithfield, London EC1A 7BE, United Kingdom
SOURCE: Cancer Chemotherapy and Pharmacology, (1995) 37/1-2 (117-124).
ISSN: 0344-5704 CODEN: CCPHDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Etoposide is a widely used cytotoxic drug that requires complex formulation for both the i.v. and oral preparation to ensure drug stability. Data on the stability of the i.v. formulation when diluted in infusion fluids are contradictory, and there is little information on the stability of the oral preparation in gastric or intestinal fluids. The stability of both i.v. and oral etoposide was therefore evaluated in the present investigation. The stability of the i.v. preparation was investigated across a range of concentrations in infusion fluids, being determined by regular sampling for high-performance liquid chromatography (HPLC) analysis and by visual inspection. The stability of the oral preparation was studied in both artificial gastric and intestinal fluids, again with regular sampling for HPLC analysis, and the influence of pH, concentration and the addition of ethanol and bile salts on oral stability was determined. The i.v. preparation showed a marked decrease in stability with increasing drug concentration, but stability was additionally reduced in i.v. bags regularly sampled with a syringe and needle as compared with bags that were inspected visually only (minimal stability in sampled bags, 24 h at 0.5 mg/ml and 5 h at 1.0 mg/ml, as compared with 10 days and 18 h at the respective concentrations in unsampled bags). Stability was also greater at room temperature, 20-23.degree.C, as compared with 8-12.degree.C. Loss of stability was indicated by a decrease in etoposide concentration (measured by HPLC) and the appearance of a fine white precipitate, shown to be pure etoposide. Importantly, the appearance of precipitate was as sensitive as a specific HPLC assay in detecting loss of stability and was in many cases apparent when the etoposide concentration was within 5% of the starting concentration. The oral formulation also showed a marked concentration-dependent decrease in stability in artificial intestinal fluid at pH 7.5 (percentage of etoposide in solution after 2 h at 0.5, 1.0, 1.5 and 2.0 mg/ml, 94 .+-. 2%, 80 .+-. 5%, 68 .+-.

1.3% and 41 .+-. 9%, respectively). There was no concentration effect on stability in gastric fluid at pH 3.0, although stability was much greater at pH 3 and pH 5 as compared with pH 1 or in intestinal fluid at pH 7.5. Stability in artificial intestinal fluid, pH 7.5, was also significantly improved by the addition of the bile salt sodium tauroglycocholate (2 mg/ml) at etoposide concentrations of 1 ($P < 0.0001$) and 2 mg/ml ($P < 0.0001$) and by the addition of ethanol (10%, v/v) at etoposide levels of 1 ($P < 0.001$) and 2 mg/ml ($P < 0.001$). These studies clearly demonstrate the concentration-dependent stability of both the i.v. and the oral formulation of etoposide, that the appearance of precipitate is a sensitive indicator of loss of stability in i.v. fluids, and that stability in artificial intestinal fluid can be modulated by the use of other agents.

L130 ANSWER 16 OF 16 EMBASE
on STN

ACCESSION NUMBER: 94294165 EMBASE
DOCUMENT NUMBER: 1994294165
TITLE: [Parenteral preparations of water insoluble drugs]. PARENTERALE ZUBEREITUNGEN VON SCHWER WASSERLOSLICHEN WIRKSTOFFEN.
AUTHOR: Reinhart T.; Bauer K.H.
CORPORATE SOURCE: Lehrstuhl Pharmazeutische Technolog., Hermann-Herder-Strasse 9,79104 Freiburg, Germany
SOURCE: Krankenhauspharmazie, (1994) 15/9 (529-533).
ISSN: 0173-7597 CODEN: KRANDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German
SUMMARY LANGUAGE: German; English

AB There are several possibilities for the manufacturing of parenteral preparations of water insoluble drugs. Drugs containing fat emulsions, cosolvents, cyclodextrins and solubilisation agents are licensed on the market. Microsuspensions for intravasal application are being investigated and developed. The physical stability of drugs containing O/W emulsions is the predominating problem of these preparations. This must be considered for the storage of these drugs. The use of cosolvents, cyclodextrins and solubilisation agents may cause side-effects, which may be explained by hemolytic and anaphylactic reactions. The conditions for storage and application depend on the type of formulation.

```
=> fil capl; d que l38
FILE 'CAPLUS' ENTERED AT 14:32:01 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 27 Feb 2004  VOL 140 ISS 10
FILE LAST UPDATED: 26 Feb 2004  (20040226/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L2       352163 SEA FILE=CAPLUS ABB=ON  NEOPLAS?/OBI
L4            1 SEA FILE=REGISTRY ABB=ON  "RHODAMINE 123"/CN
L6          623 SEA FILE=CAPLUS ABB=ON  L4
L32       89692 SEA FILE=CAPLUS ABB=ON  CARCINOMA?/OBI OR ADENOCARCINOMA?/OBI
L33       14201 SEA FILE=CAPLUS ABB=ON  PROSTAT?/OBI(L)L2
L37          92 SEA FILE=CAPLUS ABB=ON  L6(L)(THU OR BAC OR PAC OR DMA)/RL
L38          12 SEA FILE=CAPLUS ABB=ON  L37 AND (L32 OR L33)


=> s l38 not (l3 or l8 or l18 or l30)

L131         10 L38 NOT (L3 OR L8 OR L18 OR L30)

=> fil medl; d que l88
```

previously printed

```
FILE 'MEDLINE' ENTERED AT 14:32:02 ON 27 FEB 2004

 FILE LAST UPDATED: 25 FEB 2004 (20040225/UP).  FILE COVERS 1958 TO DATE.

 On December 14, 2003, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description
 on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L43       40478 SEA FILE=MEDLINE ABB=ON  PROSTATIC NEOPLASMS+NT/CT
L52        6388 SEA FILE=MEDLINE ABB=ON  L43(L)DT/CT
L57         868 SEA FILE=MEDLINE ABB=ON  RHODAMINE 123/CT
L81      289958 SEA FILE=MEDLINE ABB=ON  CARCINOMA+NT/CT
L84        3532 SEA FILE=MEDLINE ABB=ON  RHODAMINES+NT/CT
```

DT = drug therapy

```
L87          354 SEA FILE=MEDLINE ABB=ON  L84(L)(PD OR AD OR TU)/CT
L88           20 SEA FILE=MEDLINE ABB=ON  L87 AND L57 AND (L52 OR (L81(L)DT/CT))
```

PD = pharmacology
AD = administration & dosage
TU = therapeutic use

```
=> s l88 not 159

L132         17 L88 NOT L59
```

previously printed

```
=> fil embase; d que 198

FILE 'EMBASE' ENTERED AT 14:32:03 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

 FILE COVERS 1974 TO 26 Feb 2004 (20040226/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L90        1247 SEA FILE=EMBASE ABB=ON  RHODAMINE 123/CT
L91         155 SEA FILE=EMBASE ABB=ON  L90(L)(AD OR CB OR CM OR CR OR DO OR
               DT OR DB OR PD OR PR)/CT
L94       39270 SEA FILE=EMBASE ABB=ON  PROSTATE TUMOR+NT/CT
L95      283981 SEA FILE=EMBASE ABB=ON  CARCINOMA+NT/CT
L97       39843 SEA FILE=EMBASE ABB=ON  (L94 OR L95)(L)(DT OR PC)/CT
L98           7 SEA FILE=EMBASE ABB=ON  L91 AND L97
```

AD - administration
CB - drug combination
CM - drug comparison
CR - " concentration
DO - dosage
DT - drug therapy
~~DB~~
PD - pharmacology
PR - pharmaceutics
PC - prevention

```
=> s 198 not (192 or l104 or 193)

L133          6 L98 NOT (L92 OR L104 OR L93)
```

previously printed

```
=> fil drugu; d que l111

FILE 'DRUGU' ENTERED AT 14:32:05 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE LAST UPDATED: 25 FEB 2004       <20040225/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


L105          6 SEA FILE=DRUGU ABB=ON  ARCADI J?/AU
L106        179 SEA FILE=DRUGU ABB=ON  RHODAMINE-123 *PH/CT
L107       6240 SEA FILE=DRUGU ABB=ON  PROSTATE-DISEASE/CT
L108      61718 SEA FILE=DRUGU ABB=ON  CARCINOMA/CT OR ADENOCARCINOMA/CT
L110          5 SEA FILE=DRUGU ABB=ON  L106 AND L107 AND L108
L111          2 SEA FILE=DRUGU ABB=ON  L110 NOT L105


=> s l111 not l105

L134          2 L111 NOT L105
```

previously printed

```
=> fil wpids; d que l119

FILE 'WPIDS' ENTERED AT 14:32:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE LAST UPDATED:          26 FEB 2004      <20040226/UP>
MOST RECENT DERWENT UPDATE:     200414        <200414/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE


>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM
    DERWENT UPDATE 200403.
    THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.
    SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
    FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<



L114          31 SEA FILE=WPIDS ABB=ON  RHODAMINE 123 OR RHODAMINE123 OR RH123
L117        9466 SEA FILE=WPIDS ABB=ON  ?CARCINOM?
L119           4 SEA FILE=WPIDS ABB=ON  L114 AND (LL15 OR L117)


=> s l119 not l120

L135           3 L119 NOT L120

=> dup rem l132,l134,l131,l133,l135
FILE 'MEDLINE' ENTERED AT 14:33:03 ON 27 FEB 2004

FILE 'DRUGU' ENTERED AT 14:33:03 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'CAPLUS' ENTERED AT 14:33:03 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 14:33:03 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE 'WPIDS' ENTERED AT 14:33:03 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT
PROCESSING COMPLETED FOR L132
PROCESSING COMPLETED FOR L134
PROCESSING COMPLETED FOR L131
PROCESSING COMPLETED FOR L133
PROCESSING COMPLETED FOR L135
L136          33 DUP REM L132 L134 L131 L133 L135 (5 DUPLICATES REMOVED)
                 ANSWERS '1-17' FROM FILE MEDLINE
                 ANSWERS '18-19' FROM FILE DRUGU
```

previously printed

ANSWERS '20-28' FROM FILE CAPLUS
ANSWERS '29-30' FROM FILE EMBASE
ANSWERS '31-33' FROM FILE WPIDS

=> d ibib ed ab hitrn 1-33

L136 ANSWER 1 OF 33 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001296974 MEDLINE
DOCUMENT NUMBER: 21271669 PubMed ID: 11377803
TITLE: Delocalized lipophilic cations selectively target the mitochondria of carcinoma cells.
AUTHOR: Modica-Napolitano J S; Aprille J R
CORPORATE SOURCE: Department of Biology, Merrimack College, 315 Turnpike Street, North Andover, MA 01845, USA.. jnapolitano@merrimack.edu
SOURCE: Adv Drug Deliv Rev, (2001 Jul 2) 49 (1-2) 63-70. Ref: 65
Journal code: 8710523. ISSN: 0169-409X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802
ED Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802
AB Traditional chemotherapies, aimed at DNA replication in rapidly dividing cells, have achieved only limited success in the treatment of carcinomas due largely to their lack of specificity for cells of tumorigenic origin. It is important, therefore, to investigate treatment strategies aimed at novel cellular targets that are sufficiently different between normal cells and cancer cells so as to provide a basis for selective tumor cell killing. Delocalized lipophilic cations (DLCs) are concentrated by cells and into mitochondria in response to negative inside transmembrane potentials. The higher plasma and/or mitochondrial membrane potentials of carcinoma cells compared to normal epithelial cells account for the selective accumulation of DLCs in carcinoma mitochondria. Since most DLCs are toxic to mitochondria at high concentrations, their selective accumulation in carcinoma mitochondria and consequent mitochondrial toxicity provide a basis for selective carcinoma cell killing. Several of these compounds have already displayed some degree of efficacy as chemotherapeutic agents in vitro and in vivo. The effectiveness of DLCs can also be enhanced by their use in photochemotherapy or combination drug therapy. Discovery of the biochemical differences that account for the higher membrane potentials in carcinoma cells is expected to lead to the design of new DLCs targeted specifically to those differences, resulting in even greater selectivity and efficacy for tumor cell killing.

L136 ANSWER 2 OF 33 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 94328862 MEDLINE
DOCUMENT NUMBER: 94328862 PubMed ID: 8052065
TITLE: Dose response of human tumor cells to rhodamine 123 and laser phototherapy.
AUTHOR: Saxton R E; Haghighat S; Plant D; Lufkin R; Soudant J; Castro D J
CORPORATE SOURCE: Division of Surgical Oncology, UCLA School of Medicine 90024.
CONTRACT NUMBER: DC 00031 (NIDCD)
SOURCE: LARYNGOSCOPE, (1994 Aug) 104 (8 Pt 1) 1013-8.

Journal code: 8607378. ISSN: 0023-852X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19940914
Last Updated on STN: 19990129
Entered Medline: 19940907
ED Entered STN: 19940914
Last Updated on STN: 19990129
Entered Medline: 19940907
AB Previous studies have shown that Rhodamine 123 (Rh123) is an efficient tumor targeting agent for argon laser photodynamic therapy in vitro. Effectiveness of this approach for cancer treatment in vivo will depend on Rh123 tumor uptake kinetics and laser energy delivery via fiberoptics to the tumor site. In the present study, tumor and normal cells were exposed in vitro to 1 micrograms/mL Rh123 until 10%, 50%, and 100% of maximum uptake was achieved. Laser treatment response was monitored by trypan blue exclusion for tumor cell viability and by MTT tetrazolium assays to measure mitochondrial dehydrogenase activity. TE671 fibrosarcoma cells were highly sensitive to argon laser phototherapy (514 nm, 5 W, 1 minute, Tmax = 8 degrees C), with mitochondrial inhibition seen after Rh123 uptake of 12, 50, and 100 ng/million cells. P3 squamous cell carcinoma cells were inhibited 20% and 75% by the laser after Rh123 uptake of 13 or 30 ng/million cells, respectively. M26 melanoma cells were not sensitive to the laser after 15 ng/million cells Rh123 uptake but were inhibited 45% and 75% after Rh123 uptake of 80 and 160 ng/million cells. Micro2 fibroblast mitochondrial activity was reduced less than 25% by the laser after Rh123 uptake of 50 ng/million cells. Cell viability after maximum Rh123 uptake and laser treatment was decreased to 30%, 15%, and 2% for M26 melanoma, P3 squamous cell carcinoma, and TE671 fibrosarcoma cells, but remained over 80% for Micro2 fibroblasts. The results suggest that Rh123 laser treatment response depends on tumor type and drug uptake level, with normal cells being much less sensitive to phototherapy.

L136 ANSWER 3 OF 33 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 93148806 MEDLINE
DOCUMENT NUMBER: 93148806 PubMed ID: 8426526
TITLE: Absence of rhodamine 123-photochemotoxicity in human tumor xenografts.
AUTHOR: Ris H B; Altermatt H J; Schaffner T; Lim C K; Potter W R; Althaus U
CORPORATE SOURCE: Department of Thoracic and Cardiovascular Surgery, Medical School, University of Berne, Inselspital, Switzerland.
SOURCE: LASERS IN SURGERY AND MEDICINE, (1993) 13 (1) 40-4.
Journal code: 8007168. ISSN: 0196-8092.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930312
Last Updated on STN: 19990129
Entered Medline: 19930304
ED Entered STN: 19930312
Last Updated on STN: 19990129
Entered Medline: 19930304
AB Rhodamine 123 (R123)-photochemotoxicity was assessed in BALB/c nude mice bearing a xenografted human squamous cell carcinoma at various power densities and wavelengths and a given incident fluence of 150 Joules/cm2. One hour before light delivery, 1 mg R123/kg was injected i.p. in 20 animals. Surface irradiance was performed on the tumor and an equal size

hind leg area of 40 animals. Three groups of 10 animals were treated at 514.5 nm and 0.1 W/cm2, 1 W/cm2, and 30 W/cm2, and one at 488 nm and 30 W/cm2. In each group, five animals received R123. The R123 concentration was measured in the tumor (0.023 +/- 0.007 micrograms/g) and tumor-free tissue (0.023 +/- 0.008 micrograms/g) in three additional animals by high performance liquid chromatography 1 hour after R123-administration. Histologic assessment 72 hours after light delivery revealed no tissue damage at nonthermal power densities, either in the tumor or in the tumor-free tissue, irrespective of R123-administration. At 30 W/cm2, neither in the tumor nor in tumor-free tissues was there any significant difference in the depth of necrosis, irrespective of R123-administration and the wavelength applied. Our results question the validity of R123 as a photosensitizer, at least in this rodent tumor model.

L136 ANSWER 4 OF 33 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 83067410 MEDLINE
DOCUMENT NUMBER: 83067410 PubMed ID: 7146897
TITLE: Rhodamine-123 selectively reduces clonal growth of carcinoma cells in vitro.
AUTHOR: Bernal S D; Lampidis T J; Summerhayes I C; Chen L B
SOURCE: SCIENCE, (1982 Dec 10) 218 (4577) 1117-9.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198301
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19990129
Entered Medline: 19830107
ED Entered STN: 19900317
Last Updated on STN: 19990129
Entered Medline: 19830107
AB Rhodamine-123, a cationic laser dye, markedly reduced the clonal growth of carcinoma cells but had little effect on nontumorigenic epithelial cells in vitro. This selective inhibitory effect of Rhodamine-123 on some carcinomas is unusual since known anticancer drugs, such as arabinosyl cytosine and methotrexate, have not been shown to exhibit such selectivity in vitro.

L136 ANSWER 5 OF 33 MEDLINE on STN
ACCESSION NUMBER: 2003360505 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12893210
TITLE: Enhancement of sensitivity to cisplatin by orobol is associated with increased mitochondrial cytochrome c release in human ovarian carcinoma cells.
AUTHOR: Isonishi Seiji; Saitou Misato; Yasuda Makoto; Ochiai Kazunori; Tanaka Tadao
CORPORATE SOURCE: Department of Obstetrics/Gynecology, Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105, Japan.
SOURCE: Gynecologic oncology, (2003 Aug) 90 (2) 413-20.
Journal code: 0365304. ISSN: 0090-8258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030802
Last Updated on STN: 20030903
Entered Medline: 20030902
ED Entered STN: 20030802
Last Updated on STN: 20030903

Entered Medline: 20030902

AB OBJECTIVES: Based on our previous report showing that orobol, a potent phosphatidylinositol 4-kinase (PI4K) inhibitor, produced cisplatin (DDP) sensitivity, we have determined the mechanism of orobol-sensitization effect. METHODS AND RESULTS: Orobol produced >2-fold DDP sensitivity in human ovarian carcinoma 2008 cells and its DDP-resistant variant 2008/C13*5.25 cells (C13). Because orobol had no effect on conventional mechanisms such as DDP accumulation or cellular metallothionein and glutathione content, we have focused on the apoptotic signaling pathway. Orobol induced a significant increase in apoptosis in DDP-treated cells, as estimated by frequency of condensed nuclear chromatin with Hoechst 33342 stain, although orobol alone did not have any effect on apoptotic potential. The caspase-3-inhibiting peptide Ac-DEVD-CHO completely inhibited the orobol sensitization effect but did not block DDP cell cytotoxicity per se. Orobol rendered both of these cells resistant to rhodamine 123 (Rh) by more than 2.5-fold, indicating significant decrease of mitochondrial membrane potential (DeltaPsim). Confocal laser microscopy of cells stained with the mitochondria (MT)-specific dye Rh revealed that orobol decreased Rh-fluorescent intensity. Electron microscopy of these cells showed that orobol induced swelling and condensation of MT. Orobol suppressed both naturally expressed and the DDP-induced Bcl-2 expression significantly. Orobol and DDP treatment reduced cytochrome c level in MT determined by Western blot analysis, indicating increased amount of cytochrome c release from MT, whereas orobol alone did not alter the amount of cytochrome c in MT. CONCLUSIONS: These results indicate that orobol produced DDP sensitivity in human ovarian carcinoma cells by inducing apoptosis through the MT-dependent signaling pathway.

L136 ANSWER 6 OF 33 MEDLINE on STN
ACCESSION NUMBER: 2001284931 MEDLINE
DOCUMENT NUMBER: 21110946 PubMed ID: 11172601
TITLE: Differential sensitization by orobol in proliferating and quiescent human ovarian carcinoma cells.
AUTHOR: Shiotsuka S; Isonishi S
CORPORATE SOURCE: Department of Obstetrics/Gynecology, Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105, Japan.. fl1444@leo.bekkoame.ne.jp
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (2001 Feb) 18 (2) 337-42.
Journal code: 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010524

ED Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010524

AB The object of this study was to determine how phosphatidylinositol (PI) signaling pathway is involved in the regulation of cisplatin (DDP) sensitivity. Clonogenic survival assay was used to determine the effect of orobol, a potent PI4-kinase inhibitor, on DDP sensitivity in human ovarian carcinoma 2008 cells. Orobol enhanced sensitivity to DDP in 2008 cells by a factor of 2.1+/-0.4 (SD)-fold (N=3; P<0.01). Sensitization was specific for proliferating cells. Orobol did not alter DDP sensitivity in quiescent cells. Orobol also produced a 2-fold increase in sensitivity to DDP in proliferating 2008/C13*5.25 DDP-resistant variants. Our studies indicated that orobol-induced sensitization depended on the presence of proliferating cells in G2+M phase of the cell cycle. Orobol did not

modulate the cellular accumulation of DDP nor did it alter the CdCl2 sensitivity, suggesting that the amount of platinated-DNA was not changed by orobol treatment. However, orobol rendered 2008 cells resistant to rhodamin 123 by 5.7+/-1.7 (SD)-fold (N=3, P<0.01). Since sensitivity to rhodamin 123 is indicative of mitochondrial membrane potential, these results imply that mitochondrial alterations may be an important component of the orobol sensitization effect in these cells.

L136 ANSWER 7 OF 33 MEDLINE on STN
ACCESSION NUMBER: 97234470 MEDLINE
DOCUMENT NUMBER: 97234470 PubMed ID: 9079744
TITLE: Multidrug resistance in androgen-independent growing rat prostate carcinoma cells is mediated by P-glycoprotein.
AUTHOR: Siegsmund M J; Kreukler C; Steidler A; Nebe T; Kohrmann K U; Alken P
CORPORATE SOURCE: Department of Urology, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Germany.
SOURCE: UROLOGICAL RESEARCH, (1997) 25 (1) 35-41.
Journal code: 0364311. ISSN: 0300-5623.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970825
Last Updated on STN: 19990129
Entered Medline: 19970813
ED Entered STN: 19970825
Last Updated on STN: 19990129
Entered Medline: 19970813
AB Prostate carcinomas are in general resistant against virtually all cytotoxic drugs. Up to now it has not been thoroughly evaluated whether specific resistance factors, such as the expression of the MDR1 gene, play a role in this multi-agent resistance and whether there is a link between drug resistance and hormone-independent growth. We investigated the resistance patterns of a hormone-sensitive and four hormone-independent Dunning rat carcinoma sublines against four drugs which are substrates of P-glycoprotein (vinblastine, taxol, doxorubicin, and etoposide) and two agents (methotrexate and cis-platinum) which are not transported by this efflux pump. All hormone-insensitive sublines, AT.1, AT. 3.1., MatLu and Mat LyLu, continuously showed a clearly enhanced resistance (3- to 26-fold) against the P-glycoprotein substrates, compared to the hormone-sensitive subline G. Only two of the androgen-independent sublines displayed enhanced resistance against methotrexate, whereas all of them were more sensitive against cisplatin than the androgen-sensitive G cells. By addition of verapamil the resistance against vinblastine (9- to 10-fold) and taxol (6.7- to 26.7-fold) in the hormone-insensitive cells could be almost totally reversed. Furthermore, the fluorescent P-glycoprotein substrate rhodamine-123 was effectively pumped out of the four tested hormone-independent cell lines, whereas the hormone-sensitive G cells were unable to extrude the dye. By reverse transcriptase polymerase chain reaction (RT-PCR) with primers specific for the rat mdr1b gene, the homologue to the human MDR1 gene, we could easily detect mdr1b expression in the androgen independent cell lines, but not in the G cells. Our results suggest that the product of the rat mdr1b gene is involved in the multidrug resistance of androgen-independent Dunning prostate carcinoma cells.

L136 ANSWER 8 OF 33 MEDLINE on STN
ACCESSION NUMBER: 94016944 MEDLINE
DOCUMENT NUMBER: 94016944 PubMed ID: 8105110
TITLE: Role of the MDR-1-encoded multiple drug resistance phenotype in prostate cancer cell lines.

AUTHOR: Theyer G; Schirmbock M; Thalhammer T; Sherwood E R; Baumgartner G; Hamilton G
CORPORATE SOURCE: Department of Urology, Wilhelminenspital, Vienna, Austria.
SOURCE: JOURNAL OF UROLOGY, (1993 Nov) 150 (5 Pt 1) 1544-7. Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19990129
Entered Medline: 19931112

ED Entered STN: 19940117
Last Updated on STN: 19990129
Entered Medline: 19931112

AB The treatment of advanced metastatic prostate cancer by hormone manipulation or orchiectomy is frequently followed by the appearance of hormone-insensitive and highly chemoresistant tumor cells. In this study we have investigated the contribution of the P-glycoprotein-mediated drug efflux (multidrug-resistance; MDR) to the cellular resistance of prostate carcinoma-derived cell lines to diverse cytotoxic drugs by detection of P-glycoprotein (P-gp) measurement of P-gp-mediated drug transport and reversal of MDR by chemosensitizers. The in vitro chemosensitivity of three prostate cancer cell lines (PC-3, DU-145 and LNCaP) to doxorubicin was measured in a thymidine incorporation proliferation assay. Growth of the partially hormone-sensitive cell line LNCaP is inhibited by low doses of doxorubicin (IC50:27 ng./ml.), but PC-3 and DU-145 are highly resistant to the drug, with IC50 values of 10 micrograms./ml. and 7.5 micrograms./ml., respectively. The chemosensitivity of the PC-3 and DU-145 cells is increased in response to 1 microM. verapamil, 1 micrograms./ml. cyclosporine A and 2 microM. tamoxifen, which are known to partially reverse the MDR phenotype in other resistant tumors. A verapamil-sensitive drug efflux has been demonstrated for the PC-3 and Du-145, but not for the LNCaP, cell lines, using flow cytometric measurements of the P-gp substrate rhodamine 123 efflux from preloaded cells. In agreement with the functional measurements, the expression of the P-glycoprotein was detected in the PC-3 and Du-145 cell lines in Western blots using the monoclonal C 219 antibody. In conclusion, the chemoresistant and hormone-insensitive PC-3 and Du-145 cell lines express P-gp and exhibit verapamil-sensitive drug efflux, indicative of MDR. However, the low MDR-reversal rates observed in these cell lines in response to chemosensitizers in clinically achievable concentrations (approximately 2- to 3-fold reversal), point to non-MDR-associated cellular mechanisms as dominant factors of chemoresistance in prostate cancer.

L136 ANSWER 9 OF 33 MEDLINE on STN
ACCESSION NUMBER: 93218976 MEDLINE
DOCUMENT NUMBER: 93218976 PubMed ID: 8464635
TITLE: The synergistic effects of rhodamine-123 and merocyanine-540 laser dyes on human tumor cell lines: a new approach to laser phototherapy.
AUTHOR: Castro D J; Saxton R E; Haghighat S; Reisler E; Plant D; Soudant J
CORPORATE SOURCE: Division of Otolaryngology-Head and Neck Surgery, UCLA School of Medicine 90024-1624.
CONTRACT NUMBER: DC 00031 (NIDCD)
SOURCE: OTOLARYNGOLOGY - HEAD AND NECK SURGERY, (1993 Mar) 108 (3) 233-42. Journal code: 8508176. ISSN: 0194-5998.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 19990129
Entered Medline: 19930430

ED Entered STN: 19930521
Last Updated on STN: 19990129
Entered Medline: 19930430

AB Many new photosensitizers and laser wavelengths are being tested to improve photodynamic therapy by enhancing specific tumor uptake and/or retention, lowering systemic toxicity, and increasing laser tissue penetration. In this study the potential synergistic effects of rhodamine-123 (Rh-123) and merocyanine-540 (MC-540) sensitization of human tumor cell lines after laser exposure were explored. In a first series of experiments, the kinetics of uptake of Rh-123 and M-540 were tested on three human leukemia cell lines (K562, RAJI, 729HF2), P3 squamous carcinoma, and M26 melanoma. Our results demonstrate a clear difference in the rate and amount of uptake of MC-540 (K562 > P3 > RAJI > 729HF2 > M26) and Rh-123 (P3 > RAJI > 729HF2 > K562 > M26) by these cell lines. In a second series of experiments, M26 tumor cells were sensitized with either Rh-123 (1 microgram/ml) or with MC-540 (20 micrograms/ml) alone or with a combination of the two dyes for 60 minutes, then exposed to the argon (514.5 nm) laser at nonthermal energy levels. Our results demonstrate a significant enhancement of the tumoricidal effects of the laser on M26 carcinoma cells after sensitization with both dyes together (MC-540 and Rh-123) when compared to each dye alone. As with combination antibiotherapy, the synergistic effects of two laser dyes that have different intracellular targeting sites appear to enhance tumoricidal effects significantly after exposure to a matching laser wavelength. The data provide evidence for effective laser phototherapy by dye synergy.

L136 ANSWER 10 OF 33 MEDLINE on STN
ACCESSION NUMBER: 92114657 MEDLINE
DOCUMENT NUMBER: 92114657 PubMed ID: 1731162
TITLE: Laser dyes for experimental phototherapy of human cancer: comparison of three rhodamines.
AUTHOR: Haghighat S; Castro D J; Lufkin R B; Fetterman H R; Castro D J; Soudant J; Ward P H; Saxton R E
CORPORATE SOURCE: Division of Head and Neck Surgery (Otolaryngology), UCLA School of Medicine 90024-1624.
CONTRACT NUMBER: DC 00031 (NIDCD)
SOURCE: LARYNGOSCOPE, (1992 Jan) 102 (1) 81-7.
Journal code: 8607378. ISSN: 0023-852X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920308
Last Updated on STN: 19990129
Entered Medline: 19920218

ED Entered STN: 19920308
Last Updated on STN: 19990129
Entered Medline: 19920218

AB The mitochondrial dye Rhodamine 123 (Rh-123) has been shown to be an effective photosensitizer for argon-laser irradiation of some types of human cancer cells in vitro. We reported that 514.5-nm laser illumination of Rh-123 sensitized human melanoma, and squamous carcinoma cells strongly inhibited tumor-cell proliferation as measured by decreased 3H-thymidine (3H-T) uptake in vitro and may eradicate some tumors when grown as transplants in nude mice. However, several other human tumors were resistant to Rh-123 laser therapy in vitro and in vivo. In the current

study, it was possible to obtain 100- to 1000-fold increased sensitivity to 514.5-nm laser illumination by replacement of Rh-123 with the cationic rhodamine dyes Rh-3G and Rh-6G. Cell viability was decreased over 95% and 3H-T incorporation reduced at least 80% by laser phototherapy after sensitizing tumor cells with 1 micrograms/mL Rh-123, 0.01 microgram/mL Rh-3G, or 0.001 microgram/mL Rh-6G. However, Rh-123 alone did not decrease 3H-T uptake significantly unless present at over 10- to 100-fold higher levels than Rh-3G, respectively. The tumor cell dye uptake level was measured by N-butanol extraction and absorption scans at 400 to 600 nm. The results revealed that dye uptake was more rapid, and retention of Rh-3G and Rh-6G was 5- to 10-fold higher than for Rh-123 in the human tumor cells. The data suggest that Rh-3G and Rh-6G may be highly sensitive chromophores for laser phototherapy of human cancer cells.

L136 ANSWER 11 OF 33 MEDLINE on STN
ACCESSION NUMBER: 89288049 MEDLINE
DOCUMENT NUMBER: 89288049 PubMed ID: 2736534
TITLE: Rhodamine dyes as potential agents for photochemotherapy of cancer in human bladder carcinoma cells.
AUTHOR: Shea C R; Chen N; Wimberly J; Hasan T
CORPORATE SOURCE: Wellman Laboratories of Photomedicine, Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston 02114.
SOURCE: CANCER RESEARCH, (1989 Jul 15) 49 (14) 3961-5.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19990129
Entered Medline: 19890803
ED Entered STN: 19900309
Last Updated on STN: 19990129
Entered Medline: 19890803
AB The phototoxicity in vitro of rhodamine 123 and tetrabromo rhodamine 123 (TBR) was compared, in order to assess their photochemotherapeutic potential. Exposure to 514.5-nm radiation from an argon ion laser caused phototoxicity in MGH-U1 bladder carcinoma cells previously treated with either dye at 10 microM for 30 min. As assessed by colony formation and cellular morphology, TBR was markedly more phototoxic than rhodamine 123, reflecting increased intersystem crossing of TBR to the triplet manifold via spin-orbital coupling induced by the heavy bromine atoms. Photoreactions of TBR very efficiently generated singlet oxygen (1O2) in solution; furthermore, irradiation of TBR-treated cells was significantly more toxic when performed in the presence of deuterium oxide, an enhancer of damage caused by 1O2. Retention of fluorescence in TBR-treated cells was enhanced by irradiation, indicating that a stable photoproduct may be formed in reaction with cellular components.

L136 ANSWER 12 OF 33 MEDLINE on STN
ACCESSION NUMBER: 88164836 MEDLINE
DOCUMENT NUMBER: 88164836 PubMed ID: 3349477
TITLE: Anticarcinoma activity of rhodamine 123 against a murine renal adenocarcinoma.
AUTHOR: Herr H W; Huffman J L; Huryk R; Heston W D; Melamed M R; Whitmore W F Jr
CORPORATE SOURCE: Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York 10021.
SOURCE: CANCER RESEARCH, (1988 Apr 15) 48 (8) 2061-3.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198805
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19990129
Entered Medline: 19880512

ED Entered STN: 19900308
Last Updated on STN: 19990129
Entered Medline: 19880512

AB The mitochondria of carcinoma cells retain the permeant cationic compound rhodamine 123 longer than the mitochondria of normal epithelial cells. The possibility of exploiting this difference in the chemotherapy of a murine renal adenocarcinoma was investigated. Rhodamine 123 exhibited anticarcinoma activity in mice and this activity was potentiated by 2-deoxyglucose and methylglyoxal bis(guanylhydrazone), a chemotherapeutic agent that is toxic to mitochondria. Prolonged retention of rhodamine 123 by renal tumor cells compared with normal renal epithelial cells was demonstrated by flow cytometry, perhaps explaining its antitumor activity. A combination of both mitochondrial toxins, rhodamine 123 and methylglyoxal bis(guanylhydrazone) produced the longest survival and had the greatest antitumor effect.

L136 ANSWER 13 OF 33 MEDLINE on STN
ACCESSION NUMBER: 88335358 MEDLINE
DOCUMENT NUMBER: 88335358 PubMed ID: 3138616
TITLE: Phototherapy with argon lasers and Rhodamine-123 for tumor eradication.
AUTHOR: Castro D J; Saxton R E; Fetterman H R; Castro D J; Ward P H
CORPORATE SOURCE: Division of Head and Neck Surgery, UCLA School of Medicine 90024.
SOURCE: OTOLARYNGOLOGY - HEAD AND NECK SURGERY, (1988 Jun) 98 (6) 581-8.
Journal code: 8508176. ISSN: 0194-5998.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198810
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19990129
Entered Medline: 19881024

ED Entered STN: 19900308
Last Updated on STN: 19990129
Entered Medline: 19881024

AB The effectiveness of Rhodamine-123 (Rh-123) as a new photochemosensitizing agent for the argon laser treatment of human melanoma and squamous carcinoma cells in vitro was recently demonstrated. In this study, a new technique of "rosette" treatment with the argon laser was developed to completely eradicate human squamous carcinoma (P3) tumor transplants in nude mice after chemosensitization with Rh-123. Each group included four nu/nu mice injected subcutaneously with 10(7) P3 carcinoma cells/site for a total of 48 sites. Tumor take was greater than 95% at one week, with greater than 10 mm3 tumor volume at each site. Test groups were sensitized with Rh-123 (1 microgram/ml for 1 hour) by intratumor or intraperitoneal injection at 1 week and then treated with the argon laser at 514.5 nm. To allow uniform delivery of energies to the tumor and its edges, a new "rosette" technique was developed. The tumors were then exposed to nonthermal levels of 700 J/cm2 (36 degrees C) or 950 J/cm2 (40 degrees C) as determined by a new and reproducible method of dosimetry. All 16 tumors in this test group showed complete regression with excellent wound healing at 2 weeks and no recurrences, even after an 8 week followup. These results demonstrate that effective eradication of tumors

can be achieved in vivo only after sensitization with Rh-123 and specific argon laser treatment ("rosette"), even at nonthermal levels of energies. The high effectiveness of this technique and low toxicity of Rh-123 may render its clinical use very attractive for the treatment of superficial malignancies.

L136 ANSWER 14 OF 33 MEDLINE on STN
ACCESSION NUMBER: 88024471 MEDLINE
DOCUMENT NUMBER: 88024471 PubMed ID: 3663344
TITLE: Rhodamine 123 as a chemosensitizing agent for argon laser therapy. A new technique for treatment of superficial malignancies.
AUTHOR: Castro D J; Saxton R E; Fetterman H R; Castro D J; Ward P H
CORPORATE SOURCE: Division of Head and Neck Surgery, UCLA School of Medicine 90024.
SOURCE: ARCHIVES OF OTOLARYNGOLOGY -- HEAD AND NECK SURGERY, (1987 Nov) 113 (11) 1176-82.
Journal code: 8603209. ISSN: 0886-4470.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198711
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19990129
Entered Medline: 19871124
ED Entered STN: 19900305
Last Updated on STN: 19990129
Entered Medline: 19871124
AB Rhodamine 123 (Rh 123), a mitochondrial-specific dye with an absorption maxima at 511 nm, was tested as a new chemosensitizing agent for argon laser treatment of P3 human squamous carcinoma cells. After exposure of P3 cells in vitro to Rh 123 at doses of 1, 3, 6, and 10 micrograms/mL for one hour, we observed significant inhibition of DNA synthesis, except at the lowest dose. Rhodamine 123 at 1 microgram/mL was selected to sensitize P3 tumor cells for treatment with the monochromatic argon laser at 514.5 nm. Exposure of P3 cells to laser energy levels of 700 to 950 J/cm2 (36 degrees C to 40 degrees C) after sensitization with Rh 123 completely inhibited tumor development of the P3 cells transplanted subcutaneously into nude mice. Control P3 cells treated with the laser alone at 36 degrees C to 40 degrees C or only with Rh 123 formed visible tumors by one week and continued to grow for the entire-week observation period. These results show that Rh 123 is a highly sensitive new fluorochrome for argon laser phototherapy of human squamous carcinoma cells.

L136 ANSWER 15 OF 33 MEDLINE on STN
ACCESSION NUMBER: 87200606 MEDLINE
DOCUMENT NUMBER: 87200606 PubMed ID: 3573900
TITLE: Rhodamine-123 as a new photochemosensitizing agent with the argon laser: "nonthermal" and thermal effects on human squamous carcinoma cells in vitro.
AUTHOR: Castro D J; Saxton R E; Fetterman H R; Castro D J; Ward P H
SOURCE: LARYNGOSCOPE, (1987 May) 97 (5) 554-61.
Journal code: 8607378. ISSN: 0023-852X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198706
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19990129
Entered Medline: 19870605

AUTHOR: Bernal S D; Lampidis T J; McIsaac R M; Chen L B
CONTRACT NUMBER: CA22427 (NCI)
CA29793 (NCI)
CA33847 (NCI)
SOURCE: SCIENCE, (1983 Oct 14) 222 (4620) 169-72.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198311
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19990129
Entered Medline: 19831123
ED Entered STN: 19900319
Last Updated on STN: 19990129
Entered Medline: 19831123
AB Carcinoma cells and normal epithelial cells differ in the mitochondrial retention of a permeant cationic compound, rhodamine 123. The possibility of utilizing this difference in carcinoma chemotherapy was investigated. Rhodamine 123 exhibited anticarcinoma activity in mice, and this activity was potentiated by 2-deoxyglucose.

L136 ANSWER 18 OF 33 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1994-09868 DRUGU M P
TITLE: Ketoconazole Effectively Reverses Multidrug Resistance in Highly Resistant KB Cells.
AUTHOR: Siegsmund M J; Cardarelli C; Aksentijevich I; Sugimoto Y; Pastan I; Gottesman M M
CORPORATE SOURCE: Nat.Inst.Health-Bethesda; Nat.Cancer-Inst.Bethesda
LOCATION: Bethesda, Maryland, United States
SOURCE: J.Urol. (151, No. 2, 485-91, 1994) 6 Fig. 1 Tab. 34 Ref.
CODEN: JOURAA ISSN: 0022-5347
AVAIL. OF DOC.: Laboratory of Cell Biology, DCBDC, National Cancer Institute, Building 37, Room 1B22, National Institutes of Health, Bethesda, Maryland 20892, U.S.A. (M.M.G.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Ketoconazole reversed vinblastine (Sigma-Chem.) and doxorubicin resistance in the multidrug-resistant human carcinoma cell line, KB-V1, and had little effect on the parental cell line, KB-3-1. Ketoconazole or verapamil enhanced rhodamine-123 accumulation by KB-V1 cells and colchicine (Sigma-Chem.) resistant KB-8-5 cells. Low level MDR1 expression was detected in 8/11 prostate carcinoma specimens, suggesting a possible role of the gene in drug resistance. 2/3 Non-MDR1-expressing and 1/8 MDR1-expressing carcinomas were pretreated with orchiectomy, cyproterone acetate, and flutamide, respectively. It is concluded that ketoconazole is a potent reversing agent of P-glycoprotein mediated multidrug resistance in KB-V1 cells, and may overcome resistance to cytotoxic drugs in clinical situations, particularly in primary hormone-sensitive relapsing tumors.

L136 ANSWER 19 OF 33 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1985-42817 DRUGU P S
TITLE: Treatment of Experimental Prostatic Cancer with Rhodamine 123.
AUTHOR: Isaacs W B; Isaacs J T
LOCATION: Baltimore, Maryland, United States
SOURCE: Proc.Am.Assoc.Cancer Res. (26, 76 Meet., 252, 1985) 1 Ref.
ISSN: 0197-016X
AVAIL. OF DOC.: Oncology Center and Department of Urology, The Johns Hopkins

ED Entered STN: 19900303
Last Updated on STN: 19990129
Entered Medline: 19870605

AB A human squamous carcinoma cell line (P3) was first exposed to a nontoxic dose of Rhodamine-123 (1 microgram/ml for 1 hour), then subjected to treatment with a single mode argon laser at 514.5 nm. The temperature and energy levels delivered to the target cells were determined by a reproducible method of dosimetry. Cell viability was assessed by the trypan blue exclusion test. Cell duplication and DNA synthesis were measured by the incorporation of 3H-thymidine at 6 and 24 hours post-treatment. The results indicate that Rhodamine-123 at nontoxic doses of 1 microgram/ml enhanced the tumoricidal effects of the argon laser at reduced temperatures as low as 40 degrees C. Furthermore, at physiological temperature ranges as low as 28 to 39 degrees C, an immediate and/or delayed inhibition of cell duplication was demonstrated, while cell viability was not affected. These observations, suggest that Rhodamine-123 can be used effectively as a chemosensitizing agent in the treatment of human tumor cells with the argon laser at 514.5 nm. This new technique of tumor cell targeting by Rhodamine sensitization and specific laser treatment may offer real advantages without the extreme photosensitivity associated with hematoporphyrin derivatives.

L136 ANSWER 16 OF 33 MEDLINE on STN
ACCESSION NUMBER: 86198943 MEDLINE
DOCUMENT NUMBER: 86198943 PubMed ID: 3701443
TITLE: Laser photochemotherapy of rhodamine-123 sensitized human glioma cells in vitro.
AUTHOR: Powers S K; Pribil S; Gillespie G Y 3rd; Watkins P J
SOURCE: JOURNAL OF NEUROSURGERY, (1986 Jun) 64 (6) 918-23.
Journal code: 0253357. ISSN: 0022-3085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198606
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19990129
Entered Medline: 19860616

ED Entered STN: 19900321
Last Updated on STN: 19990129
Entered Medline: 19860616

AB The photochemotherapeutic effect of the mitochondria-specific dye rhodamine-123 (Rh-123) on human glioma cells in culture was studied. Cultured U-251MG glioma cells were incubated for 30 minutes in 10 micrograms/ml of Rh-123 and then exposed to blue-green light between 488 and 514.5 nm using a continuous-wave argon laser. Cells that were treated with Rh-123 and the argon laser at power densities less than 200 mW/sq cm demonstrated increasing tumor-cell killing with increasing time of exposure to laser light. Tumor-cell killing achieved with power densities of light less than 200 mW/sq cm was shown to be due solely to a photochemical effect and not to a direct (thermal) effect of the laser. The photochemical effect was dependent upon the intracellular concentration of Rh-123 and the length of light exposure, and not the intensity of light. The selective retention of Rh-123 by glioma cells and its exclusion from normal cells in conjunction with its photoactivated cytotoxicity suggest that Rh-123 may be a useful photosensitizing drug for the treatment of malignant gliomas in situ.

L136 ANSWER 17 OF 33 MEDLINE on STN
ACCESSION NUMBER: 84017536 MEDLINE
DOCUMENT NUMBER: 84017536 PubMed ID: 6623064
TITLE: Anticarcinoma activity in vivo of rhodamine 123, a mitochondrial-specific dye.

University School of Medicine, Baltimore, MD 21205, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The cytostatic activity of rhodamine 123 (Rh123) combined with 2-deoxy-glucose (2-DG) was studied in the Dunning R-3327-G rat prostatic adenocarcinoma model. Substantial reduction of tumor volume was achieved. Toxicity was high with i.p. administration but was lower with s.c. injection. (abstract).

L136 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 1996:126837 CAPLUS
DOCUMENT NUMBER: 124:219562
TITLE: Effects of rhodamine 123 on the cell growth of human prostate **carcinoma** cells in vitro and in vivo
AUTHOR(S): Yoshie, Tohru
CORPORATE SOURCE: Dep. Urol., Nara Med. Univ., Kashihara, 634, Japan
SOURCE: Nara Igaku Zasshi (1995), 46(5), 439-52
CODEN: NAIZAM; ISSN: 0469-5550
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
ED Entered STN: 01 Mar 1996
AB The suppressive effect of rhodamine 123 (Rh) on the growth of cultured prostate carcinoma cells (PC-3 and LNCaP) was examd. in vitro and in vivo. Rh suppressed the growth of PC-3 and LNCaP cells significantly. The accumulation and retention of Rh in PC-3 cells was demonstrated both in vitro and in PC-3 tumor cells implanted in nude mice. Methylglyoxal Bis(guanylhydrazone) (MGBG) and 2-deoxy-D-glucose (2 DG) suppressed the growth of PC-3 and LNCaP cells when each was administered in combination with Rh. These agents seem to modulate the suppressing effect of Rh on the growth of tumor cells. These results indicate that Rh has the potential to be an anticancer agent against prostate carcinomas.
IT **62669-70-9**, Rhodamine 123
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effects of rhodamine 123 on cell growth of human prostate **carcinoma** cells and its combination effects with deoxyglucose and guanylhydrazone)

L136 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:754203 CAPLUS
DOCUMENT NUMBER: 137:257633
TITLE: Molecular conjugates for use in treatment of cancer, and preparation thereof
INVENTOR(S): McChesney, James D.; Chander, Madhavi C.; Siahaan, Teruna J.; Xu, Christine R.
PATENT ASSIGNEE(S): Napro Biotherapeutics, Inc., USA
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002076448	A1	20021003	WO 2002-US9417	20020325

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002198141 A1 20021226 US 2002-107543 20020325
EP 1383492 A1 20040128 EP 2002-723632 20020325
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
NO 2003004166 A 20031120 NO 2003-4166 20030919
PRIORITY APPLN. INFO.: US 2001-278243P P 20010323
WO 2002-US9417 W 20020325

OTHER SOURCE(S): MARPAT 137:257633
ED Entered STN: 04 Oct 2002
AB The invention provides mol. conjugates [R1ZC(O)YCH(=N-)]nP [n = conjugation no.; P = carrier mol. (e.g. protein) moiety; R1 = moiety of biol. active mol. or its analogs, derivs., salts or secondary amines; Z = O, NH; Y = (un)branched C1-20 alkyl optionally substituted with .gtoreq.1 Ph, cycloalkyl optionally substituted with .gtoreq.1 alkyl or Ph, arom. group optionally substituted with .gtoreq.1 alkyl, electron-withdrawing or electron-donating groups]. Compds. and methods useful in producing such mol. conjugates are also provided, as well as methods of concg. biol. active mols. in selected target cells of a patient that comprise administering to the patient a selected dose of such mol. conjugates. Prepn. of conjugates of transferrin with e.g. paclitaxel derivs., and detn. of their antitumor activity, are included.
IT **62669-70-9D**, Rhodamine 123, transferrin conjugates
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(mol. conjugate prepn. for use in treatment of cancer)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:157495 CAPLUS
DOCUMENT NUMBER: 136:205412
TITLE: Oligopeptide-based prodrugs activated by plasmin and their use in cancer chemotherapy
INVENTOR(S): Trouet, Andre; Dubois, Vincent; Passioukov, Alexandre
PATENT ASSIGNEE(S): Coulter Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002015700	A1	20020228	WO 2001-US26476	20010823

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001086727 A5 20020304 AU 2001-86727 20010823
PRIORITY APPLN. INFO.: US 2000-227686P P 20000824
WO 2001-US26476 W 20010823

OTHER SOURCE(S): MARPAT 136:205412
ED Entered STN: 01 Mar 2002
AB A prodrug, cleavable by plasmin, comprises a therapeutic agent capable of entering a target cell, e.g., a tumor or inflammatory cell, an oligopeptide having a plasmin peptide substrate of 2-4 amino acids and mono- or di-peptide linkage, a stabilizing group and, optionally, a linker group. Also disclosed are methods of making and using the prodrug compds. For example, the activity of D-Ala-Leu-Lys-Leu-Leu-doxorubicin (I) (prepn. given) was evaluated in the B16-B16 murine melanoma model. The mice receiving the prodrug did not show any important wt. loss during the expt. and no clin. signs of toxicity were obsd. At the same time, the drug had a marked effect on the metastatic growth. At 34.5 .mu.mol/kg, I reduced the spread of lung metastases with a decrease of the ratio of the surface occupied by B16-B16 colonies to the non-affected one to 8.2.+-.1.8% ($P<0.01$), compared to 45.7.+-.12.6% and 44.0.+-.6.3% for non-treated and doxorubicin (5.2 .mu.mol/kg)-treated animals. The same prodrug at 69.0 .mu.mol/kg provided 1.5.+-.0.6% of surface affected.
IT **62669-70-9**, Rhodamine 123
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(oligopeptide-based prodrugs activated by plasmin for chemotherapy)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:100205 CAPLUS
DOCUMENT NUMBER: 136:379621
TITLE: Impact of BCRP/MXR, MRP1 and MDR1/P-glycoprotein on thermoresistant variants of atypical and classical multidrug resistant cancer cells
AUTHOR(S): Stein, Ulrike; Lage, Hermann; Jordan, Andreas; Walther, Wolfgang; Bates, Susan E.; Litman, Thomas; Hohenberger, Peter; Dietel, Manfred
CORPORATE SOURCE: Max-Delbruck-Center for Molecular Medicine, Berlin, 13092, Germany
SOURCE: International Journal of Cancer (2002), 97(6), 751-760
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 06 Feb 2002
AB The impact of the ABC transporters breast cancer resistance protein/mitoxantrone resistance assocd. transporter (BCRP/MXR), multidrug resistance-assocd. protein 1 (MRP1) and multidrug resistance gene-1/P-glycoprotein (MDR1/PGP) on the multidrug resistance (MDR) phenotype in chemoresistance and thermoresistance was investigated in the parental human gastric carcinoma cell line EPG85-257P, the atypical MDR subline EPG85-257RNOV, the classical MDR subline EPG85-257RDB and their thermoresistant counterparts EPG85-257P-TR, EPG85-257RNOV-TR and EPG85-257RDB-TR. Within the atypical MDR subline EPG85-257RNOV expression of BCRP/MXR and of MRP1 were clearly enhanced (vs. parental and classical MDR lines). MDR1/PGP expression was distinctly elevated in the classical MDR subline EPG85-257RDB (vs. parental and atypical MDR sublines). In all thermoresistant counterparts basal expression of BCRP/MXR, MRP1 and MDR1/PGP was increased relative to thermosensitive sublines. Although it could be shown that the overexpressed ABC transporters were functionally active, however, no decreased drug accumulations of doxorubicin, mitoxantrone and rhodamine 123 were obsd. Thus, expression of BCRP/MXR, MRP1 and MDR1/PGP was found to be dependent on the appropriate type of chemoresistance; correlating with a classical or atypical MDR phenotype. Within the thermoresistant variants, however, the increase in ABC transporter expression did obviously not influence the MDR phenotype.
IT **62669-70-9**, Rhodamine 123
RL: PKT (Pharmacokinetics); **THU (Therapeutic use)**; BIOL

(Biological study); USES (Uses)
(BCRP/MXR, MRP1 and MDR1/P-glycoprotein impact on thermoresistant variants of atypical and classical multidrug resistant cancer cells)
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:157444 CAPLUS
DOCUMENT NUMBER: 136:365849
TITLE: Photosensitizer accumulation in spontaneous multidrug resistant cells: a comparative study with Rhodamine 123, Rose Bengal acetate and Photofrin
AUTHOR(S): Croce, Anna C.; Supino, Rosanna; Lanza, Karen S.; Locatelli, Donata; Baglioni, Piero; Bottiroli, Giovanni
CORPORATE SOURCE: Centro Studio Istochimica, CNR and Dip. Biologia Animale, Universita Pavia, Pavia, Italy
SOURCE: Photochemical & Photobiological Sciences (2002), 1(1), 71-78
CODEN: PPSHCB; ISSN: 1474-905X
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 01 Mar 2002
AB The influence both of overexpression of multidrug transporter proteins and of phenotype changes occurring in cells developing spontaneous resistance on the accumulation of photosensitizer mols. was studied on two tumor-derived cell lines (B16, A2780) expressing the MDR-1 phenotype. Rhodamine 123, Rose Bengal acetate (a fluorogenic substrate that is restored to the native active mol. by specific enzyme activity inside cells) and Photofrin were considered. The two resistant variants accumulate Rhodamine 123 to a lesser extent than the resp. wild types. Treatment with verapamil markedly enhances Rhodamine 123 accumulation in resistant cells, blocking the drug extrusion. The amt. of Rose Bengal is larger in resistant cells than in wild type cells. Verapamil does not affect drug accumulation, although it significantly impairs the efflux process. The results are explained by the enhancement of both membrane traffic and esterase activity resulting in intracellular Rose Bengal prodn. that counterbalances the increased ability in the outward transport of resistant cells. Photofrin is accumulated to a lower degree in resistant than in wild type cells. Verapamil does not alter the drug accumulation, although the release process is somewhat affected. Different intracellular turnovers of Photofrin take place in the cell variants, and the release of the monomeric fluorescent fractions is greater in resistant than in wild type cells.
IT **62669-70-9**, Rhodamine 123
RL: PKT (Pharmacokinetics); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(photosensitizer accumulation in spontaneous multidrug resistant cells: Rhodamine 123 vs. Rose Bengal acetate vs. Photofrin)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:126410 CAPLUS
DOCUMENT NUMBER: 128:188616
TITLE: Assay for multidrug resistance based on fluorescent dye exclusion
INVENTOR(S): Eytan, Gera; Assaraf, Yehuda
PATENT ASSIGNEE(S): Technion Research and Development Foundation Ltd., Israel; Friedman, Mark, M.; Eytan, Gera; Assaraf, Yehuda
SOURCE: PCT Int. Appl., 46 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807034	A1	19980219	WO 1997-US14083	19970812
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9741477	A1	19980306	AU 1997-41477	19970812

PRIORITY APPLN. INFO.: IL 1996-119066 19960814
WO 1997-US14083 19970812

ED Entered STN: 02 Mar 1998
AB A reliable and quantifiable measure of multidrug resistance is provided which is based on a functional assay of fluorescent dye exclusion from cells. The selection of a fluorescent substrate having slow transmembrane movement results in an improved assay overcoming many of the shortcomings of existing MDR assays.
IT **62669-70-9**, Rhodamine 123
RL: BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(multidrug resistance assay based on fluorescent dye exclusion)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:754268 CAPLUS
DOCUMENT NUMBER: 130:162813
TITLE: The effect of rhodamine-123 on 3 prostate tumors from the rat
AUTHOR(S): Arcadi, John A.
CORPORATE SOURCE: Huntington Medical Research Institutes, Pasadena, CA, USA
SOURCE: Journal of Urology (Baltimore) (1998), 160(6, Pt. 2), 2402-2406
CODEN: JOURAA; ISSN: 0022-5347
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 Dec 1998
AB Rhodamine-123 (Rh-123) was found to have a specific attraction to the mitochondria of tumor cells. The destruction of rat prostate tumor cells by Rh-123 is described. Tissue was used from rat prostate studies of Rh-123 treatment of R3327-H, PA III prostate tumor of Pollard and the autochthonous tumor in Lobund-Wistar rats. All tissues were fixed in 10% buffered formalin, paraffin embedded and sectioned at 1 to 3 .mu.. for good cellular detail. Destructive processes were seen in all 3 rat prostate tumor models evaluated. The changes included acinar cell clumping, acinar destruction with scarring, cyst formation within acinar cells and increased stromal cells. Since all tumor models were found to respond to Rh-123 in a similar manner, any of them could be used for the evaluation of anticancer agents. These studies demonstrated that Rh-123 was effective in suppressing the growth of hormone sensitive and insensitive rat prostate tumor cells.

IT **62669-70-9**, Rhodamine-123
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of rhodamine-123 on 3 prostate tumors from the rat)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:377089 CAPLUS
DOCUMENT NUMBER: 125:49345
TITLE: Compounds, pharmaceutical composition and diagnostic system comprising same, and their use
INVENTOR(S): Trouet, Andre; Baurain, Roger
PATENT ASSIGNEE(S): La Region Wallonne, Belg.; Baurain, Roger
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9605863	A1	19960229	WO 1995-BE76	19950821
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
BE 1008580	A3	19960604	BE 1994-751	19940819
BE 1008581	A3	19960604	BE 1994-752	19940819
CA 2203622	AA	19960229	CA 1995-2203622	19950821
AU 9532486	A1	19960314	AU 1995-32486	19950821
AU 694546	B2	19980723		
EP 769967	A1	19970502	EP 1995-928905	19950821
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10508291	T2	19980818	JP 1995-507662	19950821
NO 9700748	A	19970410	NO 1997-748	19970218
US 5962216	A	19991005	US 1997-793910	19970401
US 6342480	B1	20020129	US 1999-298330	19990423
US 2002160943	A1	20021031	US 2001-12576	20011109

PRIORITY APPLN. INFO.:
BE 1994-751 A 19940819
BE 1994-752 A 19940819
WO 1995-BE76 W 19950821
US 1997-793910 A1 19970401
US 1999-298330 A1 19990423

OTHER SOURCE(S): MARPAT 125:49345
ED Entered STN: 29 Jun 1996
AB The compds. W-Z-M of the invention comprise an element M, selected from markers and therapeutic agents having an intracellularly active site, linked to a ligand W-Z having an arm Z linked to a terminal group W. The bond between the arm Z of the ligand W-Z and the element M prevents the compd. (W-Z-M) from penetrating within the cells and/or inhibits expression of the marker M. This bond is selectively cleaved by factors secreted by target cells so as to enable the marker M to be expressed in the target cells or the therapeutic agent M to penetrate therein; the terminal group W ensures that the compd. (W-Z-M) is stable in serum and circulating blood. Data are presented for e.g. effect of .beta.-Ala-L-Leu-L-Ala-L-Leu-daunorubicin conjugate with mammary carcinoma cells. Also described is characterization of protease(s) secreted into

the extracellular medium and able to hydrolyze .beta.-Ala-Leu-Ala-Leu-doxorubicin.

IT **62669-70-9D**, Rhodamine 123, conjugates with linker arm and terminal group
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(drug conjugates and marker conjugates with cleavable bond, pharmaceutical compns., and diagnostic system)

L136 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:500606 CAPLUS
DOCUMENT NUMBER: 122:255732
TITLE: Relationship of multidrug resistance to rhodamine-123 selectivity between **carcinoma** and normal epithelial cells: taxol and vinblastine modulate drug efflux
AUTHOR(S): Brouty-Boye, Daniele; Kolonias, Despina; Wu, Chun Jing; Savaraj, Niramol; Lampidis, Theodore J.
CORPORATE SOURCE: School Medicine, Univ. Miami, Miami, FL, 33101, USA
SOURCE: Cancer Research (1995), 55(8), 1633-8
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 20 Apr 1995
AB Preferential retention and cytotoxicity of Rhodamine-123 (Rho-123) was originally reported in a no. of carcinoma cell types isolated from a variety of tissues as compared to normal epithelial cells from a limited no. of other tissues. In the present study, we have calcd. Rho-123 selectivity in normal and tumor cell lines isolated from the same tissue source, i.e., human breast. We found that: (a) in matched pairs of normal and carcinoma breast cells, Rho-123 displays no preferential retention in either cell type; (b) there is no preferential toxicity in carcinoma as compared to normal breast cells; in fact, one of the carcinoma cell lines (MDA-MB231) shows moderate resistance to this dye; (c) all of the human breast cell lines do not express P-glycoprotein-mediated multidrug resistance; (d) the normal monkey kidney epithelial cell line CV-1, which was originally used as a model to demonstrate the relative resistance of normal epithelial cells to this drug, is found to express high levels of the mdr-1 gene, is resistant to other multidrug-resistant drugs (taxol and vinblastine), and its resistance to Rho-123 as well as decreased Rho-123 retention can be reversed by verapamil; and (e) taxol and vinblastine are found to block increased Rho-123 efflux in CV-1 cells. Thus, overall the data suggest that preferential retention and cytotoxicity of Rho-123 in carcinoma vs. normal epithelial cells is related to the differential expression of the mdr-1 gene.

IT **62669-70-9**, Rhodamine-123
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(rhodamine-123 preferential retention and cytotoxicity in **carcinoma** vs. normal epithelial cells in relation to mdr-1 gene differential expression and taxol and vinblastine modulation)

L136 ANSWER 29 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 92185768 EMBASE
DOCUMENT NUMBER: 1992185768
TITLE: Rhodamine-123 as a new chemosensitizing versus toxic agent on human squamous carcinoma cells and fibroblast cultures.
AUTHOR: Castro D.J.; Saxton R.E.; Fetterman H.R.; Castro D.J.; Ward P.H.
CORPORATE SOURCE: Division of Head and Neck Surgery, UCLA School of Medicine,Los Angeles, CA 90024-1624, United States
SOURCE: Journal of Clinical Laser Medicine and Surgery, (1992) 10/2

(83-90).
ISSN: 1044-5471 CODEN: JCLSEO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Rhodamine-123 is a specific dye with an absorption maxima at 511 nm which was tested as a potential chemosensitizing agent for laser treatment of tumor cells. Because Rhodamine, at high doses, has direct cytotoxic effects on human cells in the absence of laser exposure, we tested the human squamous P3 carcinoma cell line and two normal fibroblast cell lines for sensitivity to various levels of this dye. These cells were exposed to Rhodamine-123 at concentrations of 1, 3, 6, and 10 .mu.g/ml for 1, 8, and 24 hours. The results indicate that Rhodamine-123 is nontoxic to human P3 carcinoma cells and normal fibroblast cultures at concentrations equal or lower than 1 .mu.g/ml. However, at concentrations equal or higher than 3 .mu.g/ml, a significant immediate and/or delayed inhibition of cell duplication was demonstrated. The results show that Rhodamine-123 at 1 .mu.g/ml can be used to sensitize tumor cells for targeting by monochromatic 514.5 nm Argon lasers.

L136 ANSWER 30 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 89265754 EMBASE
DOCUMENT NUMBER: 1989265754
TITLE: Rhodamine-123 as a new laser dye: In vivo study of dye effects on murine metabolism, histology and ultrastructure.
AUTHOR: Castro D.J.; Saxton R.E.; Rodgerson D.O.; Fu Y.S.; Bhuta S.M.; Fetterman H.R.; Castro D.J.; Tartell P.B.; Ward P.H.
CORPORATE SOURCE: Division of Head and Neck Surgery, UCLA School of Medicine, Los Angeles, CA 90024-1624, United States
SOURCE: Laryngoscope, (1989) 99/10 I (1057-1062).
ISSN: 0023-852X CODEN: LARYA8
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
011 Otorhinolaryngology
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Rhodamine-123 (Rh-123) is a mitochondrial-specific dye that has recently proven to be an effective fluorochrome for photodynamic therapy of squamous carcinoma cells and melanomas with the Argon laser. Complete eradication of heterotransplanted human tumors in nude mice was possible if tumors were first 'sensitized' to Rh-123 and then treated with the Argon laser. Prior to initiation of human testing of this technique, the toxicity and pathological changes in BALB/c mice were tested by an escalating dose schedule after systemic injection of Rh-123. Animals' body weight, blood chemistry, enzymes and organ evaluation for histology, and ultrastructural changes were analyzed for 3 weeks after injection with Rh-123. The results of this study demonstrate that Rh-123 has significant systemic toxicity in BALB/c mice injected at doses of 10 .mu.g/g of body weight and above, manifested by chronic weight loss and elevation of muscle enzymes with death of the animals injected at doses higher than 50 .mu.g/g of body weight. At doses of 1 .mu.g/g of Rh-123, no local or systemic toxicity was observed even after a 3-week follow-up, suggesting that safe and effective tumor sensitization might be possible in humans at this concentration. The high effectiveness of this new technique of

photodynamic therapy and the low toxicity of this dye in this preclinical model system suggests that Rh-123 and the Argon laser may represent a powerful new method for treatment of superficial malignancies.

L136 ANSWER 31 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-507897 [54] WPIDS
DOC. NO. CPI: C2002-144363
TITLE: New aryl-indane compounds or their diastereomers, enantiomers or salts useful in the treatment of tumor.
DERWENT CLASS: B05
INVENTOR(S): MELIKIAN-BADALIAN, A
PATENT ASSIGNEE(S): (AVLA-N) AVLAN LTD; (MELI-I) MELIKIAN-BADALIAN A
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002030915	A2	20020418	(200254)*	EN	87

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2002024372 A 20020422 (200254)
US 2002128231 A1 20020912 (200262)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002030915	A2	WO 2001-US32017	20011011
AU 2002024372	A	AU 2002-24372	20011011
US 2002128231	A1 Provisional	US 2000-240345P	20001011
		US 2001-976929	20011011

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002024372	A Based on	WO 2002030915

PRIORITY APPLN. INFO: US 2000-240345P 20001011; US 2001-976929 20011011
ED 20020823
AB WO 200230915 A UPAB: 20020823
NOVELTY - Aryl-indane compounds or their diastereomers, enantiomers or salts are new.
DETAILED DESCRIPTION - Aryl-indane compounds of formula (I) or their diastereomers, enantiomers or salts are new.
R1, R2 = -OR9 or -NR10R11;
R3 - R8 = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl (all optionally substituted by COOH, OH, CO(CH2)nCH3, CO(CH2)n, CH2N(R12)2 or halogen), H, 1-10C alkoxy, phenyl, phenoxy, benzyl(oxy), 3-8C cycloalkyl, N(R12)2, NHCOR13, S(O)q(1-10C)alkyl, OH or halogen;
R3 + R4, R4 + R5, R6 + R7 or R7 + R8 = -O-A-O on contiguous carbon;
R9 = T1, 2-10C alkylidene, phenylene (all optionally substituted by at least one of T2 or halogen), alkylsilyl, arylsilyl or alkylarylsilyl;
T1 = 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene;
T2 = OH, COOH, alkoxy, NHR12, N(R12)2 or NHCOR13;
R10, R11 = T1, S(O)q(R14), C(O)NH(R14), C(O)q(R14), phenylene or benzylene (all optionally substituted by at least one of T2 or a group of formula 4-R15,R16 di-substituted piperidinyl, 3-R15,R16 di-substituted

azetidinyl, 3-R15,R16 di-substituted pyrrolidinyl, 5-R15-substituted azocanyl, 4-R15-substituted piperidinyl, 4-R15 substituted piperazinyl, 8-R17-substituted 1,3,8-triaza-spiro(4.5)decan-4-one-1-yl, a group of formula (i), 8-R17 substituted-2,8-diaza-spiro(4.5)decane-1-yl or 2,3,4,5-tetrahydro-1H-benzo(d)azepine-3-yl;

R12 = H, T3 or aryl (all optionally substituted by at least one of T4);

T3 = 1-10C alkyl, 2-10C alkenyl or benzyl;

T4 = OH, COOH, NH2, secondary amine, tertiary amine, tetrazole or PO3H2;

R13 = T3 or aryl (all optionally substituted by at least one of T4);

R14 = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl (all optionally substituted by COOH, CO(CH2)nCH3 or OH), 3-6C cycloalkyl, phenyl or benzyl;

R15, R16 = H, aryl, 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl (all optionally substituted by at least one of CH2OH, N(R12)2, NHCOR13, OH or halogen);

aryl = naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl or pyrimidyl (all optionally substituted by at least one of R17, R18 or R19);

R17 - R19 = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl (all optionally substituted by COOH, CO(CH2)nCH3, CO(CH2)n, CH2N(R14)2, OH or halogen), phenyl, benzyl, 3-8C cycloalkyl, 1-10C alkoxy, S(O)q(1-10C)alkyl, N(R14)2, NHCOR6, OH, H or halogen;

X and Y = -CH2-, -(CH2)2-, -(CH2)3-, C=O, CH2C(O), (CH2)2C(O), CH2SO2 or (CH2)2SO2;

q = 0 - 3;

n = 0 - 6; and

a = single or double bond;

when R15 occurs without R16, R15 is not H.

N.B. A is not defined.

INDEPENDENT CLAIMS are also included for the following:

(1) increasing bioavailability of an orally administered pharmaceutical compound;

(2) treating tumor (drug-resistant) in a mammal involving coadministering (I) and a therapeutic agent; and

(3) delivering a pharmaceutical compound to the central nervous system of a patient involving coadministering the pharmaceutical compound with (I).

ACTIVITY - Antitumor; Cytostatic.

MECHANISM OF ACTION - P-glycoprotein-mediated (P-gp) transport inhibitor; Multidrug resistance modulator.

Parental NIH3T3 Swiss mouse embryo cell line was grown in Dulbecco's Modified Eagles Medium supplemented with glucose (4.5 g/l), 10% fetal bovine serum, L-glutamine (2 mM) and gentamicin (0.01 mg/ml). Drug resistant NIH3T3 cells were derived by transfection of the human MDR1 cDNA into parental NIH3T3 cells and were maintained in similar medium supplemented with colchicine (60 ng/ml). The human ileocecal adenocarcinoma cell line HCT-8 was grown on RPMI-1640 medium supplemented with 10% horse serum, sodium pyruvate (1 mM) and gentamicin (0.01 mg/ml). All cells were maintained in humidified atmosphere with 5% CO2 at 37 deg. C. Parental and MDR1-expressing NIH 3T3 cells were plated in 96-well microtiter plates and were exposed to doxorubicin (50 nM), vinblastine (7.5 nM), colchicine (75 nM) or paclitaxel (300 nM) for 72 hours. Cell viability was determined with colorimetric MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium) assay as described in Mosmann T, J. Immunol. Methods, 65:55 - 63 (1983); Hansen M B et al., J. Immunol. Methods 119:203 - 210 (1989) and the absorbance was measured at 570 nm. The efficacy of 2-(3-(3,4-dibutoxy-phenyl)-2-(4-(2-ethoxy-phenyl)-piperazine-1-carbonyl)-5,6-dibutoxy-indan-1-yl)-1-(4-(2-ethoxy-phenyl)-piperazin-1-yl)-ethanone (A) in Rhodamine 123 transport was evaluated. (A) showed 96% inhibition of

R123 transport.

USE - (I) Is used for inhibiting P-glycoprotein-mediated transport, in the treatment of multidrug resistance in tumor cells in mammals, for delivering pharmaceutical compound to central nervous system (all claimed), for modulating multidrug resistance during treatment with chemotherapeutic agents and in cancer chemotherapy.

ADVANTAGE - (I) Shows % inhibition of Rhodamine 123 transport and a % increase in cytotoxicity value of at least 30 (preferably at least 50, especially at least 80)%. (I) increases bioavailability of an orally administered pharmaceutical compound and increases sensitivity of tumor cells converted from sensitivity to therapeutic agents, to resistance to the therapeutic agents. (I) Also increases drug bioavailability by inhibiting active transport system in the gut and decreases the net transport of drug across gut epithelia, and reduces P-gp active transport across the luminal membrane to prevent the return of drugs absorbed into the cytoplasm.

Dwg.0/6

L136 ANSWER 32 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-540088 [51] WPIDS
DOC. NO. NON-CPI: N2003-428314
DOC. NO. CPI: C2003-146350
TITLE: Collapsible vena cava filter for introduction into a blood vessel of a patient comprises an apical hub, several struts secured to and diverging from the apical hub, filter media and a bioactive coating.
DERWENT CLASS: B05 B07 D22 K08 P34
INVENTOR(S): GRIFFIN, D; LEONARD, R B; MOLGAARD-NIELSEN, A; RAGHEB, A O
PATENT ASSIGNEE(S): (COOK-N) COOK INC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002193828	A1	20021219	(200351)*		9
WO 2002102436	A2	20021227	(200351)	EN	

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002193828	A1 Provisional	US 2001-298803P	20010614
		US 2002-172725	20020614
WO 2002102436	A2	WO 2002-US18923	20020614

PRIORITY APPLN. INFO: US 2001-298803P 20010614; US 2002-172725 20020614

ED 20030808

AB US2002193828 A UPAB: 20030808

NOVELTY - Collapsible vena cava filter comprises:

(1) apical hub;

(2) several struts secured to and diverging from apical hub;

(3) filter media connected to the struts and spanning the space between the struts; and

(4) a bioactive coating applied to the surfaces of the filter.

DETAILED DESCRIPTION - A collapsible vena cava filter comprises:

(I) an apical hub;

(II) several struts secured to and diverging from the apical hub, where each of the struts terminate in holding mechanisms that engage the walls of the blood vessel to secure the filter in a selected location inside the vessel;

(III) filter media connected to the struts and spanning the space between the struts; and

(IV) a bioactive coating applied to the surfaces of the filter to prevent the growth of tissue that would interfere with removal of the filter as well as medicate the patient.

The layer of bioactive material has a coated surface area of 0.1-10 (preferably 1-5, especially 3) micro g/mm2 or coating thickness of 100-300 micro g of drug per 0.001 inch.

An INDEPENDENT CLAIM is also included for a collapsible filter (F1) for introduction into a blood vessel of a patient, where the collapsible filter has a proximal portion, a medial portion and a distal portion, comprising:

(a) an apical hub, in the proximal portion of the filter, having a first or distal end and a second or proximal end;

(b) several struts having proximal end and distal end portions;

(c) a pair of side element associated with each of the struts;

(d) a deployment and retrieval section secured to and extending proximately from the second or proximal end of the apical hub; and

(e) the bioactive coating.

The proximal ends of struts are secured to the first or distal end of the apical hub.

The proximal ends diverge distally and outwardly from the hub. Each of the struts has an outwardly turned hook at their distal ends. Each side element has a proximal portion and a distal portion.

The proximal end of the proximal portions is secured to the first or distal end of the apical hub.

The proximal end diverges distally and outwardly from the hub such that the associated strut lies between the pair of side elements.

The distal portion of each side element diverges inwardly toward the associated strut such that the distal ends of the pair of side elements meet and form an eyelet through which the associated strut passes in a sliding relationship.

The filter as a whole may be unfolded from a collapsed insertion condition in which the struts and side elements form a narrow bundle for arrangement in a catheter like insertion instrument into an open tulip like filter configuration with the side elements interoposed between the struts.

USE - The collapsible vena cava filter is used for introduction into a blood vessel of a patient (claimed).

ADVANTAGE - The vena cava filter is removable from its deployed location in the vessel of the patient without trauma to the tissue of the vessel wall and without risk of tearing of intimal tissue, which could cause embolization.

DESCRIPTION OF DRAWING(S) - The drawing shows an elevation view of an endovascular filter in a fully expanded condition.

Vena cava filter 10

Apical hub body 12

Struts 14

First or distal end 16, 48

Distal end sections 18

Anchoring sections 20

Second or proximal end 23, 34

Side elements 24

Distal end portions 26

Not given 28

Retrieval section 30

Hook 31

Ferrule 32
Not given 42
Medial portion 44, 47
Proximal filter ends. 46
Dwg.1/6

L136 ANSWER 33 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1986-170865 [27] WPIDS
DOC. NO. CPI: C1986-073338
TITLE: New charged dye transition metal complexes - having antitumour activity and radiosensitising activity.
DERWENT CLASS: B05
INVENTOR(S): CHEN, L B; RICHMOND, R C; TEICHER, B A
PATENT ASSIGNEE(S): (JOHO) JOHNSON MATTHEY INC
COUNTRY COUNT: 12
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 186363	A	19860702	(198627)*	EN	12
R: AT BE CH DE FR GB IT LI LU NL SE					
US 4921973	A	19900501	(199022)		
EP 186363	B	19901114	(199046)		
R: AT BE CH DE FR GB IT LI LU NL SE					
DE 3580571	G	19901220	(199101)		
US 5196413	A	19930323	(199314)		4

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
EP 186363	A		EP 1985-308933	19851209
US 4921973	A		US 1988-186177	19880426
US 5196413	A	Cont of	US 1984-680044	19841210
		Cont of	US 1988-186158	19880426
			US 1991-660904	19910227

PRIORITY APPLN. INFO: US 1984-680044 19841210
ED 19930802
AB EP 186363 A UPAB: 19930922
A (+)-charged dye transition metal complex is new. The metal is pref. a platinum gp. metal, esp. Pt(II). The complex formed between **rhodamine-123** and Pt(II), Pt(Rh-123) is specifically claimed. The complexes are formed by reacting a (+)-charged dye with a metal cpd. USE/ADVANTAGE - The complexes demonstrate antitumour activity. The The complexes also possess radiosensitising activity whereby cells or tissues can be made more sensitive to killing effects of ionising radiation when the complexes are used before, during or after irradiation. 0/2

```
=> fil medl; d que l51; d que l53; s (l51 or l53) not (l59 or l80 or l88)
FILE 'MEDLINE' ENTERED AT 14:33:59 ON 27 FEB 2004

 FILE LAST UPDATED: 25 FEB 2004 (20040225/UP). FILE COVERS 1958 TO DATE.

 On December 14, 2003, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description
 on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

L40        8032 SEA FILE=MEDLINE ABB=ON  PROSTATE-SPECIFIC ANTIGEN/CT
L41      119866 SEA FILE=MEDLINE ABB=ON  PRETREAT? OR PRE(W)(TREAT? OR
                THERAP?) OR PRETHERAP?
L43       40478 SEA FILE=MEDLINE ABB=ON  PROSTATIC NEOPLASMS+NT/CT
L44       20026 SEA FILE=MEDLINE ABB=ON  L43(L)TH./CT  TH = therapy
L45      276232 SEA FILE=MEDLINE ABB=ON  FOLLOW-UP STUDIES/CT
L48      173845 SEA FILE=MEDLINE ABB=ON  TREATMENT OUTCOME/CT
L49        3779 SEA FILE=MEDLINE ABB=ON  L40/MAJ
L50          59 SEA FILE=MEDLINE ABB=ON  L49 AND L44 AND L45 AND L48
L51          21 SEA FILE=MEDLINE ABB=ON  L41 AND L50


L40        8032 SEA FILE=MEDLINE ABB=ON  PROSTATE-SPECIFIC ANTIGEN/CT
L43       40478 SEA FILE=MEDLINE ABB=ON  PROSTATIC NEOPLASMS+NT/CT
L45      276232 SEA FILE=MEDLINE ABB=ON  FOLLOW-UP STUDIES/CT
L48      173845 SEA FILE=MEDLINE ABB=ON  TREATMENT OUTCOME/CT
L49        3779 SEA FILE=MEDLINE ABB=ON  L40/MAJ
L52        6388 SEA FILE=MEDLINE ABB=ON  L43(L)DT/CT  - DT = drug therapy
L53           9 SEA FILE=MEDLINE ABB=ON  L52 AND L49 AND L45 AND L48


L137         29 (L51 OR L53) NOT (L59 OR L80 OR L88)

=> d ibib ab 1-29; fil hom

L137 ANSWER 1 OF 29     MEDLINE on STN
ACCESSION NUMBER:    2003585336     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 14665356
TITLE:               Comparing PSA outcome after radical prostatectomy or
                     magnetic resonance imaging-guided partial prostatic
                     irradiation in select patients with clinically localized
                     adenocarcinoma of the prostate.
AUTHOR:              D'amico Anthony V; Tempany Clare M; Schultz Delray; Cormack
                     Robert A; Hurwitz Mark; Beard Clair; Albert Michele; Kooy
                     Hanne; Jolesz Ferenc; Richie Jerome P
CORPORATE SOURCE:    Department of Radiation Oncology, Brigham and Women's
                     Hospital and Dana Farber Cancer Institute, Boston,
                     Massachusetts 02115, USA.
CONTRACT NUMBER:     R01: AG 19513-01 (NIA)
SOURCE:              Urology, (2003 Dec) 62 (6) 1063-7.
                     Journal code: 0366151. ISSN: 1527-9995.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       (EVALUATION STUDIES)
```

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20031224
Entered Medline: 20031223

AB OBJECTIVES: To determine whether high-dose radiation delivered to a subvolume of the prostate gland (peripheral zone) using intraoperative magnetic resonance imaging-guided brachytherapy provided comparable 5-year prostate-specific antigen (PSA) control rates to radical prostatectomy (RP) in select patients compared prospectively but in a nonrandomized setting. METHODS: Between 1997 and 2002, 322 and 196 patients with clinical Stage T1c, PSA less than 10 ng/mL, biopsy Gleason score 3 + 4 or less, and without perineural invasion underwent RP or intraoperative magnetic resonance imaging-guided brachytherapy, respectively, and had a 2-year minimal follow-up. Cox regression multivariable analysis was used to evaluate whether the initial therapy, **pretreatment** PSA level, biopsy Gleason score, percentage of positive biopsies, or prostate gland volume were predictors of the time to post-therapy PSA failure. PSA failure was estimated using the Kaplan-Meier method and defined using the American Society for Therapeutic Radiology Oncology consensus definition. RESULTS: Only the percentage of positive prostate biopsies (P(Cox) = 0.02) was a significant predictor of the time to post-treatment PSA failure. However, the distribution of this parameter between RP and brachytherapy-treated patients was not significantly different (P(chi-square) = 0.25). The initial therapy did not predict for the time to post-therapy PSA failure (P(Cox) = 0.18). The 5-year estimate of PSA control was 93% versus 95% (P(log-rank) = 0.16) for the RP and brachytherapy patients, respectively. CONCLUSIONS: Despite only partial prostatic irradiation using intraoperative magnetic resonance imaging-guided brachytherapy, similar 5-year estimates of PSA control were found for both brachytherapy and RP-managed patients.

L137 ANSWER 2 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003475629 MEDLINE
DOCUMENT NUMBER: 22913762 PubMed ID: 14550443
TITLE: Clinical correlates to PSA spikes and positive repeat biopsies after prostate brachytherapy.
AUTHOR: Reed Daniel; Wallner Kent; Merrick Gregory; Buskirk Steven; True Lawrence
CORPORATE SOURCE: Department of Radiation Oncology, University of Washington School of Medicine, Seattle, Washington, USA.
SOURCE: UROLOGY, (2003 Oct) 62 (4) 683-8.
Journal code: 0366151. ISSN: 1527-9995.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20031011
Last Updated on STN: 20031108
Entered Medline: 20031107

AB OBJECTIVES: To make some preliminary observations regarding the biochemical characteristics of the doubly confusing picture of prostate-specific antigen (PSA) spikes and histologically positive biopsies after prostate brachytherapy. METHODS: All patients reported here had a **pretreatment** PSA level of less than 10 ng/mL and Gleason score of 4 to 6. Transperineal iodine-125 implants (without supplemental beam radiotherapy) were performed as previously described. After implantation, patients were followed up routinely, with repeat PSA measurements and physical examinations every 4 to 6 months. The timing of the postimplant PSA measurements was at the discretion of the patients and

their doctors. No patient received preimplant or postimplant hormonal therapy. Repeat biopsies were performed from 13 to 31 months (median 22) after implant. RESULTS: Patients' prespike nadir ranged from 0.9 to 1.7 ng/mL (median 1.2). The time from the implant to the start of the spike ranged from 9 to 24 months (median 13). The time from implant to the spike peak ranged from 12 to 30 months (median 22). The peak spike height ranged from 2.6 to 8.4 ng/mL (median 3.1). Patients' last PSA value ranged from 0.1 to 0.5 ng/mL (median 0.2). CONCLUSIONS: Transient PSA rises can occur even in the presence of a persistently positive biopsy, and patients and physicians should not feel compelled to rush ahead with salvage therapy. On the basis of the patient data reported here, it appears that a spike up to 10 ng/mL is still consistent with cancer eradication.

L137 ANSWER 3 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003375142 MEDLINE
DOCUMENT NUMBER: 22791505 PubMed ID: 12909210
TITLE: Biochemical failure as a determinant of distant metastasis and death in prostate cancer treated with radiotherapy.
AUTHOR: Pollack Alan; Hanlon Alexandra L; Movsas Benjamin; Hanks Gerald E; Uzzo Robert; Horwitz Eric M
CORPORATE SOURCE: Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA.. A_Pollack@FCCC.edu
CONTRACT NUMBER: CA-06927 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (2003 Sep 1) 57 (1) 19-23.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030812
Last Updated on STN: 20031009
Entered Medline: 20031008

AB PURPOSE: Biochemical failure (BF), defined by a rising prostate-specific antigen (PSA) profile, is an early surrogate of treatment failure. However, little evidence is available to show that BF is associated with death for patents with prostate cancer treated with radiotherapy. We examined the relationship between BF and death from prostate cancer. METHODS AND MATERIALS: A total of 942 patients were treated between 1987 and 1998 with external beam radiotherapy who had sufficient PSA determinations in follow-up for the analyses described. The median radiation dose was 72 Gy, median PSA was 9.9 ng/mL, and median follow-up was 73 months. The American Society for Therapeutic Radiology and Oncology consensus definition was used to define BF. Kaplan-Meier calculations were from the start of radiotherapy. Cox proportional hazards regression multivariate analyses were used to investigate the association of BF (time-dependent variable) and other factors to distant metastasis (DM), cause-specific death (CSD), and overall death (OD). The year of treatment was included in some of the multivariate analyses to correct for potential unknown factors that may have occurred during the years of the study, such as stage migration. RESULTS: BF was observed in 316 patients (34%), and 66 (7%) experienced DM, 32 (3%) died of prostate cancer, and 230 (24%) died overall during the study period. The Kaplan-Meier 5-year rate estimates from the start of treatment for BF, DM, CSD, and OD were 38%, 6%, 3%, and 13%, respectively. All patients with DM had BF. In multivariate analyses, BF was associated with DM and CSD, but not OD. The inclusion of the year of treatment did not alter these relationships. CONCLUSION: BF, as a time-dependent covariate, was the strongest determinant of DM and was also very significantly related to CSD. The inclusion of the year of treatment had little effect on these associations. Longer follow-up is needed to determine conclusively the

relationship of BF to OD.

L137 ANSWER 4 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003155831 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12665684
TITLE: Serum markers variation consistent with autoschizis induced by ascorbic acid-menadione in patients with prostate cancer.
AUTHOR: Lasalvia-Prisco Eduardo; Cucchi Silvia; Vazquez Jesus; Lasalvia-Galante Eduardo; Golomar Wilson; Gordon William
CORPORATE SOURCE: School of Medicine, University of Uraguay, Montevideo, Uriguay.. telemedical@pharmablood.com
SOURCE: Medical oncology (Northwood, London, England), (2003) 20 (1) 45-52.
Journal code: 9435512. ISSN: 1357-0560.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030404
Last Updated on STN: 20031024
Entered Medline: 20031023

AB In vitro exposure of malignant prostate cell lines to ascorbic acid-menadione showed that tumor cells were killed through a mechanism named autoschizis. Experimental animal studies showed that autoschizis is also evident when ascorbic acid-menadione is administered to nude mice with implanted human prostate tumors. Prostate-specific antigen (PSA) is a known serum marker of prostate tumor cells specific activity. Recently, total serum homocysteine has been identified as a marker of tumor cell numbers with sensitivity for early detection of tumor cell death induced by treatments. A clinical trial with prostate cancer patients submitted to the association of ascorbic acid-menadione was performed and PSA/homocysteine was assessed in the follow- up. The early response in serum PSA and homocysteine levels was reported. The results showed that ascorbic acid-menadione produced an immediate drop in tumor cell numbers as assessed by homocysteine levels. Serum PSA levels showed an early rise and later dropped. These results suggest that autoschizis can also be induced by this pharmacological association at the clinical level in prostate cancer patients. Further studies are being performed in order to research if these results can be found with other primary tumors as it was shown in in vitro and experimental models. Ascorbic acid-menadione could be emerging as a new antitumoral chemotherapy.

L137 ANSWER 5 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003155577 MEDLINE
DOCUMENT NUMBER: 22558926 PubMed ID: 12670563
TITLE: Hormonal therapy for patients with advanced adenocarcinoma of the prostate: is there a role for discontinuing treatment after prolonged androgen suppression?.
AUTHOR: Pedraza Roberto; Kwart Arnold M
CORPORATE SOURCE: Department of Urology, Washington Hospital Center, Washington, DC 20010, USA.
SOURCE: UROLOGY, (2003 Apr) 61 (4) 770-3.
Journal code: 0366151. ISSN: 1527-9995.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308

ENTRY DATE: Entered STN: 20030403
Last Updated on STN: 20030808
Entered Medline: 20030807

AB OBJECTIVES: To determine the hormonal (luteinizing hormone [LH], testosterone) and biochemical (prostate-specific antigen [PSA]) response to withdrawal of LH-releasing hormone (LHRH) agonist therapy for patients with prostate cancer with an undetectable PSA who received this treatment for an extended period. METHODS: Four selected patients older than 70 years of age with advanced adenocarcinoma of the prostate who were treated with a depot injection of LHRH and antiandrogen therapy had their treatment discontinued. During the period of total androgen blockade, each patient obtained and maintained a persistent undetectable PSA level. After cessation of androgen blockade, patients underwent serum measurements of PSA and testosterone at baseline and then every 6 months for 36 months. Serum LH was performed at baseline and then at 6, 18, and 36 months. RESULTS: At the time androgen ablative therapy was discontinued, patients had received LHRH agonist/antiandrogen therapy for a mean of 108 months (range 94 to 120). All 4 patients had castrate levels of testosterone (less than 0.5 ng/mL) and undetectable levels of PSA at baseline and with continued monitoring. At 6 and 18 months, all patients except one had LH levels in the normal range. All 4 patients remained clinically asymptomatic throughout the follow-up period with undetectable PSA levels. CONCLUSIONS: Withdrawing hormonal therapy in asymptomatic patients with advanced prostate cancer after prolonged total androgen blockade was noted to be safe and effective in elderly patients who had achieved an undetectable PSA level. It appears that reduced testosterone levels may be a result of altered and potentially irreversible Leydig cell function rather than continued suppression of the hypothalamic-pituitary-testicular axis.

L137 ANSWER 6 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2002733305 MEDLINE
DOCUMENT NUMBER: 22383656 PubMed ID: 12496063
TITLE: Induction of apoptosis in low to moderate-grade human prostate carcinoma by red clover-derived dietary isoflavones.
AUTHOR: Jarred Renea A; Keikha Mohammad; Dowling Caroline; McPherson Stephen J; Clare Anne M; Husband Alan J; Pedersen John S; Frydenberg Mark; Risbridger Gail P
CORPORATE SOURCE: Centre for Urological Research, Monash Institute of Reproduction & Development, Monash University, Victoria 3168, Australia.
SOURCE: CANCER EPIDEMIOLOGY, BIOMARKERS AND PREVENTION, (2002 Dec) 11 (12) 1689-96.
Journal code: 9200608. ISSN: 1055-9965.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20021227
Last Updated on STN: 20030406
Entered Medline: 20030404

AB Epidemiological evidence suggests a geographical basis for the incidence of prostate cancer and dietary factors, including isoflavone consumption, may be linked to this phenomenon. This paper reports a nonrandomized, nonblinded trial with historically matched controls from archival tissue designed to determine the effects of acute exposure to a dietary supplement of isoflavones in men with clinically significant prostate cancer before radical prostatectomy. Thirty-eight patients were recruited to the study upon diagnosis of prostate cancer. Before surgery, 20 men

consumed 160 mg/day of red clover-derived dietary isoflavones, containing a mixture of genistein, daidzein, formononetin, and biochanin A. Serum PSA, testosterone, and biochemical factors were measured, and clinical and pathological parameters were recorded. The incidence of apoptosis in prostate tumor cells from radical prostatectomy specimens was compared between 18 treated and 18 untreated control tissues. There were no significant differences between pre- and posttreatment serum PSA, Gleason score, serum testosterone, or biochemical factors in the treated patients ($P > 0.05$). Apoptosis in radical prostatectomy specimens from treated patients was significantly higher than in control subjects ($P = 0.0018$), specifically in regions of low to moderate-grade cancer (Gleason grade 1-3). No adverse events related to the treatment were reported. This report suggests that dietary isoflavones may halt the progression of prostate cancer by inducing apoptosis in low to moderate-grade tumors, potentially contributing to the lower incidence of clinically significant disease in Asian men. The assessment of new prostatic therapies aimed at increasing apoptosis should control for intake of dietary isoflavones.

L137 ANSWER 7 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2002713004 MEDLINE
DOCUMENT NUMBER: 22363019 PubMed ID: 12474533
TITLE: The role of radical prostatectomy in patients with **pretreatment** prostate-specific antigen > or = 40 ng/mL.
AUTHOR: Vanasupa Bill P; Paquette Edmond L; Wu Hongyu; Sun Leon; McLeod David G; Moul Judd W
CORPORATE SOURCE: Center for Prostate Disease Research, 1530 East Jefferson Street, Rockville, Maryland 20852, USA.
SOURCE: Urol Oncol, (2002 Jul-Aug) 7 (4) 167-72.
Journal code: 9805460. ISSN: 1078-1439.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030102
Entered Medline: 20021231

AB OBJECTIVE: To assess the efficacy of radical prostatectomy (RP) in men presenting with markedly elevated prostate-specific antigen (PSA) levels, the records of 17 patients presenting with serum PSA values > or = 40 ng/mL, who underwent RP at Walter Reed Army Medical Center (WRAMC) between 1990 and 1995, were reviewed. METHODS: Pathologic and clinical data (staging, Gleason score, recurrences, adjuvant and neo-adjuvant treatment, most recent PSA value, urinary continence, and sexual function) for each patient was examined. The Kaplan-Meier method was used to analyze the disease-free survival (DFS) for PSA and clinical recurrence. Urinary continence and potency were also assessed. RESULTS: With a mean follow-up of 6.21 years (median 5.28 y), all 17 patients are alive. Five patients have no evidence of disease (NED), and 12 are alive with prostate cancer. Fifteen patients have PSA values between 0.1 and 3.0 ng/mL, and two patients have PSA values that have returned to **pretreatment** levels. Eleven patients received neo-adjuvant and/or adjuvant therapy. Fourteen men (82.3%) are continent and seven (41.1%) are potent. Survival analysis demonstrates a PSA DFS of 52.9% at five years and 26.5% at nine years; while, clinical DFS was 92.3% at five years and 58.0% at nine years. CONCLUSIONS: This study suggests a possible surgical role in treating patients presenting with significantly elevated PSA values. While surgery alone is unlikely to cure prostate cancer in these patients, surgery in conjunction with hormonal or radiation therapy may prolong survival with acceptable effects on urinary continence and potency.

L137 ANSWER 8 OF 29 MEDLINE on STN

ACCESSION NUMBER: 2002652671 MEDLINE
DOCUMENT NUMBER: 22299734 PubMed ID: 12412166
TITLE: An interinstitutional and interspecialty comparison of treatment outcome data for patients with prostate carcinoma based on predefined prognostic categories and minimum follow-up.
COMMENT: Comment in: Cancer. 2002 Nov 15;95(10):2041-3
AUTHOR: Vicini Frank A; Martinez Alvaro; Hanks Gerald; Hanlon Alex; Miles Brian; Kernan Ken; Beyers David; Ragde Haakon; Forman Jeffrey; Fontanesi James; Kestin Larry; Kovacs Gyorgy; Denis Louis; Slawin Kevin; Scardino Peter
CORPORATE SOURCE: Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, Michigan, USA.. fvicini@beaumont.edu
SOURCE: CANCER, (2002 Nov 15) 95 (10) 2126-35.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021105
Last Updated on STN: 20030202
Entered Medline: 20030131

AB BACKGROUND: The optimal management of patients with clinically localized prostate carcinoma remains undefined due in part to the absence of well-designed, prospective, randomized trials. The current study was conducted to compare and contrast outcomes with different forms of therapy for patients with prostate carcinoma who were treated at several institutions using predefined prognostic categories. METHODS: A retrospective study of 6877 men with prostate carcinoma who were treated between 1989 and 1998 at 7 different institutions with 6 different types of therapy was conducted. Five-year actuarial rates of prostate specific antigen (PSA) failure were calculated based on predefined prognostic categories, which included combinations of **pretreatment** PSA level, tumor stage, and Gleason score. In addition, outcome was calculated using consistent biochemical failure definitions and a minimum, median length of follow-up. RESULTS: Substantial differences in outcome were observed for the same type of treatment and at the same institution, depending on the number of prognostic variables used to define treatment groups. However, estimates of 5-year PSA outcomes after all forms of therapy for low-risk and intermediate-risk patient groups were remarkably similar (regardless of the type of treatment) when all three **pretreatment** variables were used to define prognostic categories. For patients in high-risk groups, the 5-year PSA outcomes were suboptimal, regardless of the treatment technique used. CONCLUSIONS: The current data suggest that interinstitutional and interspecialty comparisons of treatment outcome for patients with prostate carcinoma are possible but that results must be based on all major prognostic variables to be meaningful. Analyzed in this fashion, 5-year PSA results were similar for patients in low-risk and intermediate-risk groups, regardless of the form of therapy. Findings from prospective, randomized trials using survival (cause specific and overall) as the end point for judging treatment efficacy and longer follow-up will be needed to validate these findings and to identify the most appropriate management option for patients with all stages of disease.

L137 ANSWER 9 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2002491722 MEDLINE
DOCUMENT NUMBER: 22240444 PubMed ID: 12350483
TITLE: Predictive factor analysis as the basis for the clinical utility of percent positive prostate biopsies in patients with intermediate-risk prostate cancer.

AUTHOR: Yoon Jeong H; Chen Ming-Hui; Renshaw Andrew A; Richie Jerome P; D'Amico Anthony V
CORPORATE SOURCE: Department of Urology and Pathology, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.
SOURCE: UROLOGY, (2002 Sep) 60 (3) 454-7.
Journal code: 0366151. ISSN: 1527-9995.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020928
Last Updated on STN: 20021213
Entered Medline: 20021115

AB OBJECTIVES: To define the clinical reason for the further refinement of stratification of prostate-specific antigen (PSA) outcome using percent positive prostate biopsies in intermediate-risk patients. METHODS: A chi-square metric was used to compare the distribution of **pretreatment** clinical and post-treatment pathologic factors for patients with intermediate-risk prostate cancer with 50% or less versus greater than 50% positive prostate biopsies. The PSA outcome stratified by the percent positive biopsies was calculated according to the Kaplan-Meier actuarial method. Comparisons of actuarial PSA failure-free survival were performed using the log-rank test. RESULTS: The group with greater than 50% positive biopsies for prostate cancer had a significantly higher proportion of patients with **pretreatment** PSA values greater than 10 to 20 ng/mL ($P = 0.01$), biopsy Gleason score 4+3 ($P = 0.05$), and 1992 American Joint Committee on Cancer clinical category T2b ($P = 0.01$) than did the group with less than 50% positive biopsies. The group with greater than 50% positive biopsies also had a significantly higher proportion of patients with prostatectomy Gleason score 4+3 or higher ($P = 0.001$), pathologic Stage T3b ($P < 0.0001$), and rate of positive surgical margins ($P = 0.002$) than did the group of patients with less than 50% positive biopsies. CONCLUSIONS: The results of this study provide an explanation on the basis of the **pretreatment** and post-treatment predictive factors for the difference in PSA outcome for intermediate-risk patients when stratified by the percent positive biopsies.

L137 ANSWER 10 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2000511509 MEDLINE
DOCUMENT NUMBER: 20517816 PubMed ID: 11062386
TITLE: UsToo PC-SPES surveys: review of studies and update of previous survey results.
AUTHOR: Porterfield H
CORPORATE SOURCE: UsToo International Inc., Oak Brook, Illinois 60523, USA.. hankustoo@msn.com
SOURCE: MOLECULAR UROLOGY, (2000 Fall) 4 (3) 289-91;discussion 293.
Journal code: 9709255. ISSN: 1091-5362.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207

AB In 1997, we resolved to survey UsToo members and other men known at that time to be taking PC-SPES, a Chinese herb combination that contains eight herbs: chrysanthemum, dyers woad, licorice, reishi, san-qi ginseng, rabdosia, saw palmetto, and baikal skullcap. The survey showed positive results, with respondents experiencing a decline in serum prostate specific antigen (PSA), most to the undetectable range. Of these patients, 88% maintained a low PSA concentration, whereas 12% had a rise

from nadir. These results made it obvious that we should obtain follow-up reports from the respondents. We therefore conducted a second survey, this time finding 93% of the respondents with positive results and only 7% reporting a rise in PSA after the initial lowering with PC-SPES. Even though there are some side effects, a great majority of men are realizing good PSA control while taking the capsules, and some of the respondents are now into their fourth year of PC-SPES use. Currently, several institutions are investigating the biology of this Chinese herb combination. Although there is some estrogenic effect, there are other potential mechanisms of action to enable this product to control PSA, not only in newly diagnosed cancer, but also in longer-term use.

L137 ANSWER 11 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2000410726 MEDLINE
DOCUMENT NUMBER: 20273346 PubMed ID: 10815899
TITLE: Prognostic value of serial tissue prostate-specific antigen measurements during different hormonal treatments in prostate cancer patients.
AUTHOR: Grande M; Carlstrom K; Rozell B L; Stege R; Pousette A
CORPORATE SOURCE: Department of Woman and Child Health, Karolinska Institutet, Karolinska Hospital, Stockholm, Sweden.
SOURCE: CLINICAL CANCER RESEARCH, (2000 May) 6 (5) 1790-5. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907
Last Updated on STN: 20000907
Entered Medline: 20000829

AB To reveal the effects of different hormonal treatments directly on the prostate during treatment, the concentration of prostate-specific antigen in the tissue (T-PSA) was studied in 63 patients with untreated newly diagnosed carcinoma of the prostate (CaP). T-PSA measurements were performed in fine-needle aspiration biopsies at the time of diagnosis and 6, 12, and 24 months after initiation of treatment. Treatments modalities were bilateral orchidectomy, gonadotropin-releasing hormone (GnRH) agonists, or parenteral estrogens. Thirty-one (49%) of the patients died of CaP and 18 (29%) of other diseases. Fourteen of the patients (22%) were still alive at the end of the observation period (median follow-up time, 111.5 months; range, 98-128 months). In all of the 31 patients who died of CaP, T-PSA values increased during treatment. This increase was observed long before clinical signs of progression appeared (median of interval, 14 months). Twenty of these 31 patients showed an increase in T-PSA from **pretreatment** values at 6 months. At 12 months this increase was observed in 30 of 31 patients. In contrast, in all of the patients who responded to the hormonal regimen, T-PSA values decreased and remained low during treatment. Furthermore, the patients who did not die of CaP and received estrogen treatment had significantly higher T-PSA values compared with those who were treated with bilateral orchidectomy or GnRH agonists. This indicates that estrogens may stimulate PSA synthesis in tumor tissue in vivo in the presence of castration levels of testosterone. Statistical evaluation showed that the T-PSA ratio between month 12 and month 0 had the most significant prognostic value for predicting the clinical outcome. This ratio was superior to clinical classifications, e.g., tumor stage and cytological grade, and also was higher than T-PSA at the time of diagnosis. This study has shown that aspiration biopsy material can be used to reveal biochemical changes in the tissue during treatment and that one specific marker (T-PSA) can predict the clinical outcome of endocrine treatment of CaP patients better than previously used methods. We believe that selected tissue markers or

the protein pattern can help us to characterize the tumors and predict the clinical outcome so an optimal treatment can be chosen for every patient.

L137 ANSWER 12 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2000150698 MEDLINE
DOCUMENT NUMBER: 20150698 PubMed ID: 10687990
TITLE: Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer.
COMMENT: Comment in: J Urol. 2000 Oct;164(4):1322-3
AUTHOR: Pisansky T M; Kozelsky T F; Myers R P; Hillman D W; Blute M L; Buskirk S J; Cheville J C; Ferrigni R G; Schild S E
CORPORATE SOURCE: Department of Urology, Mayo Clinic, Rochester, Minnesota, USA.
SOURCE: JOURNAL OF UROLOGY, (2000 Mar) 163 (3) 845-50.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20020531
Entered Medline: 20000316

AB PURPOSE: Elevated serum prostate specific antigen (PSA) may be the initial and only indication of disease recurrence after prostatectomy for prostate cancer. External beam radiotherapy may be given in this setting in an attempt to eradicate the disease but therapeutic outcomes after this approach require further description. We describe the intermediate term outcome in a large group of patients treated with radiotherapy and identify **pre-therapy** factors associated with disease outcome. MATERIALS AND METHODS: We retrospectively studied a cohort of 166 consecutive patients treated with radiotherapy between July 1987 and May 1996. The Kaplan-Meier method was used to describe patient outcome for the overall study group, and statistical associations of **pre-therapy** variables with outcome were sought to identify predictive factors. RESULTS: At a median followup of 52 months 46% (95% confidence interval 38 to 55) of patients were expected to be free of biochemical relapse 5 years after radiotherapy. Multivariate analysis identified pathological classification (seminal vesicle invasion), tumor grade and preradiotherapy serum PSA as independent factors associated with biochemical relapse. Although in 1 of 6 patients a chronic complication was attributed to radiotherapy, it was often mild and self-limited in nature. CONCLUSIONS: In our current series approximately half of the patients treated with radiotherapy for an isolated elevation of serum PSA after prostatectomy were free of biochemical relapse at 5 years of followup. Radiotherapy may be given in this setting with modest long-term morbidity.

L137 ANSWER 13 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2000096210 MEDLINE
DOCUMENT NUMBER: 20096210 PubMed ID: 10632349
TITLE: The dynamics of prostate-specific antigen after definitive radiation therapy for prostate cancer.
AUTHOR: Vollmer R T; Montana G S
CORPORATE SOURCE: Department of Laboratory Medicine, Veterans Affairs Medical Center, Durham, North Carolina 27705, USA..
voll002@duke.edu
SOURCE: CLINICAL CANCER RESEARCH, (1999 Dec) 5 (12) 4119-25.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000214

AB We report the use of an exponential model for capturing the dynamics of serial measurements of prostate-specific antigen (PSA) made just before and after definitive radiation therapy of localized prostate cancer. Our study patients consisted of 164 men treated at a community hospital and without use of adjuvant hormonal therapy, and we had a mean of 5 years follow-up. We found that the model fits allowed us to condense PSA dynamic information into four parameters, including the initial **pretreatment** value of PSA, and three of these related significantly to subsequent outcome. The model also provided greater understanding of the prognosis of men with rising PSA after radiation therapy. Specifically, two of the model's parameters allowed us to compare the PSA status of these men to those with hormone-refractory disease, and we discovered that at the time of "biochemical relapse," there is a broad spectrum in expected probability of imminent death as well as in time to an adverse outcome. Thus, the model provides information that allows one to stratify men with rising PSA into a continuous spectrum from low to high risk for an adverse outcome. We believe these results show that exponential models have the potential for providing useful clinical information about men with rising PSA after definitive radiation therapy and that they could help us decide when further therapy is needed. Therefore, we recommend further study and development of these models as part of clinical research protocols involving radiation therapy of localized prostate cancer.

L137 ANSWER 14 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2000010007 MEDLINE
DOCUMENT NUMBER: 20010007 PubMed ID: 10526285
TITLE: Defining biochemical cure for prostate carcinoma patients treated with external beam radiation therapy.
AUTHOR: Kestin L L; Vicini F A; Ziaja E L; Stromberg J S; Frazier R C; Martinez A A
CORPORATE SOURCE: Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, Michigan 48073, USA.
SOURCE: CANCER, (1999 Oct 15) 86 (8) 1557-66.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991117

AB BACKGROUND: The authors retrospectively reviewed their institution's long term experience with conventional external beam radiation therapy (RT) for localized prostate carcinoma to identify criteria associated with long term biochemical cure. METHODS: Between January 1987 and December 1994, 871 patients were treated with external beam RT alone for clinically localized prostate carcinoma at William Beaumont Hospital, Royal Oak, Michigan. All patients received only external beam RT to a median total dose of 66.6 grays (Gy) (range, 59.4-70.4 Gy). No patient received hormonal therapy unless treatment failure was documented. The median follow-up was 5.0 years (range, 0. 2-11.8 years). Biochemical failure was defined according to the American Society for Therapeutic Radiology and Oncology Consensus Panel definition. RESULTS: In the entire study group, 380 patients experienced biochemical failure at a median interval of 1.5 years after the completion of RT. The 5-year and 7-year actuarial rates of biochemical control were 50% and 48%, respectively. On multivariate analysis, a higher **pretreatment** prostate specific antigen (PSA)

level, higher Gleason score, higher clinical T classification, higher nadir level, and shorter time interval to nadir all were associated significantly with biochemical failure (P < 0.001). The median intervals to biochemical failure for patients with **pretreatment** PSA levels </= 3.9 ng/mL, 4.0-19.9 ng/mL, and >/= 20.0 ng/mL were 2.2 years, 1.5 years, and 1.2 years, respectively (P < 0. 001). The median intervals to biochemical failure for patients with Gleason scores of 2-4, 5-7, and 8-10 were 1.8 years, 1.5 years, and 1.1 years, respectively (P < 0.001). Only 6 patients failed beyond 5 years after treatment even though 136 patients were at risk for failure beyond this point. When restricting analysis to 643 patients (74%) with >/= 3 years of PSA follow-up, the median nadir level for biochemically controlled patients was 0.6 ng/mL and occurred at a median interval of 1.9 years after RT versus a median nadir level of 1.3 ng/mL (P = 0.002) occurring at a median interval of 1.0 years (P < 0.001) in those patients who experienced biochemical failure. Patients were divided into subgroups based on their PSA nadir level and time to nadir. The 5-year actuarial biochemical control rates for patients with nadir values of </= 0.4 ng/mL, 0.5-0.9 ng/mL, 1. 0-1.9 ng/mL, 2.0-3.9 ng/mL, and >/= 4.0 ng/mL were 78%, 60%, 50%, 20%, and 9%, respectively (P < 0.001). The 5-year actuarial biochemical control rates for patients who reached their nadir at < 1.0 years, 1.0-1.9 years, 2.0-2.9 years, and >/= 3.0 years were 30%, 52%, 64%, and 92%, respectively (P < 0.001). All 52 patients who achieved a nadir of </= 0.4 ng/mL and required >/= 2.0 years to reach this nadir had biochemically controlled disease. CONCLUSIONS: These results suggest that a patient has a high likelihood of biochemical cure after treatment for prostate carcinoma with conventional doses of external beam RT if he has not demonstrated biochemical failure within 5 years of treatment. Patients with lower **pretreatment** PSA levels and lower Gleason scores may require longer follow-up than those with less favorable characteristics to achieve the same certainty of cure. Patients who achieve a PSA nadir </= 0.4 ng/mL and require >/= 2.0 years to reach this nadir have the highest probability of cure.

L137 ANSWER 15 OF 29 MEDLINE on STN
ACCESSION NUMBER: 1999238088 MEDLINE
DOCUMENT NUMBER: 99238088 PubMed ID: 10223577
TITLE: Outcome evaluation of the 1997 American Joint Committee on Cancer staging system for prostate carcinoma treated by radiation therapy.
AUTHOR: Iyer R V; Hanlon A L; Pinover W H; Hanks G E
CORPORATE SOURCE: Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, USA.
SOURCE: CANCER, (1999 Apr 15) 85 (8) 1816-21.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990513

AB BACKGROUND: The 1997 American Joint Committee on Cancer (AJCC) staging system condensed unilobular tumors into one entity and continues the use of both imaging and biopsy to alter classification status in T2 and T3 carcinomas. This study analyzes the biochemical freedom from disease recurrence (bNED) outcome in a large database to determine whether these changes reflect outcome differences. METHODS: Five hundred and thirty-seven patients with adenocarcinoma of the prostate were treated with radiation therapy to a median dose of 7180 centigrays (cGy) (range, 6316-8074 cGy) between November 1987 and November 1994. The median age of the patients was 70 years and the median follow-up was 51 months. The

median **pretreatment** prostate specific antigen (PSA) was 11.0 ng/mL. Patients were analyzed using 1992 AJCC stage comparing bNED outcome after radiation therapy for T2a versus T2b versus T2c tumors using Kaplan-Meier estimation and the log rank test. Patients then were analyzed multivariately using Cox regression with the known prognostic variables of dose, **pretreatment** PSA, palpation stage, and grade in addition to palpation plus imaging stage and palpation plus biopsy stage. The prognostic endpoint was bNED with failure as defined by the 1997 American Society for Therapeutic Radiology and Oncology Consensus Panel. RESULTS: The 1992 AJCC palpation classifications T2a versus T2b versus T2c have a significantly different (P = 0.02) bNED outcome. Prognostic significance is lost by pooling these three classifications in the 1997 AJCC staging system. Adding imaging information to palpation did not improve the ability of palpation alone to assess bNED status (P = 0.33). However, the addition of biopsy information to palpation significantly (P = 0.02) increased the accuracy of palpation stage alone to predict for bNED outcome for T2 and T3 tumors. CONCLUSIONS: The subdivision of T2 tumors in the 1992 AJCC classification (T2a, T2b, and T2c) should be used in the next revision of the 1997 AJCC staging system. The addition of imaging data does not discriminate bNED outcome any better than palpation stage alone in T2 and T3 tumors and should not be used. The addition of biopsy information to palpation stage did significantly improve the predicted outcome compared with palpation alone and should continue to be used.

L137 ANSWER 16 OF 29 MEDLINE on STN
ACCESSION NUMBER: 1999210245 MEDLINE
DOCUMENT NUMBER: 99210245 PubMed ID: 10195870
TITLE: Influence of luteinizing hormone-releasing hormone analogues on serum levels of prostatic acid phosphatase and prostatic specific antigen in patients with metastatic carcinoma of the prostate.
AUTHOR: Sasagawa I; Kubota Y; Nakada T; Suzuki H; Hirano J; Sugano O; Kato H; Imamura A; Mastushita K; Onmura Y; Saito M; Adachi M
CORPORATE SOURCE: Department of Urology, Yamagata University, School of Medicine, Japan.
SOURCE: INTERNATIONAL UROLOGY AND NEPHROLOGY, (1998) 30 (6) 745-53. Journal code: 0262521. ISSN: 0301-1623.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990521
AB Serum concentrations of luteinizing hormone (LH), testosterone, prostatic acid phosphatase (PAP) and prostatic specific antigen (PSA) were measured in 16 patients with advanced prostatic cancer before and after treatment with luteinizing hormone-releasing hormone (LHRH) analogue. An initial rise of serum LH and testosterone levels was observed on day 2 of the treatment. Subsequently, serum concentrations of PAP and PSA showed a transient increase on day 5 of the treatment. This indicates that LHRH analogues had better be given in combination with antiandrogens in patients with metastatic carcinoma of the prostate.

L137 ANSWER 17 OF 29 MEDLINE on STN
ACCESSION NUMBER: 1999046240 MEDLINE
DOCUMENT NUMBER: 99046240 PubMed ID: 9828800
TITLE: Is prostate specific antigen density an important prognostic indicator for patients with prostate cancer treated with external beam therapy?.

AUTHOR: Aref I; Eapen L; Agboola O; Cross P
CORPORATE SOURCE: Department of Radiation Oncology, Ottawa Regional Cancer Centre, Ontario.
SOURCE: BRITISH JOURNAL OF RADIOLOGY, (1998 Aug) 71 (848) 868-71. Journal code: 0373125. ISSN: 0007-1285.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981203

AB The purpose of this study was to determine if prostate specific antigen density (PSAD) is a predictor of outcome following external beam radiotherapy for prostate cancer, and to compare it with other prognostic factors. Between January 1990 and December 1993, 205 patients with T1-T3 adenocarcinoma of the prostate received a radical course of external beam irradiation, with no prior or adjuvant hormonal therapy. All patients had pre- and post-treatment serum prostate specific antigen (PSA) evaluation. They were followed up for at least 24 months. PSAD was defined as the ratio of **pre-treatment** serum PSA to the prostate volume, as determined from CT treatment planning scans. Prostate volumes were calculated using the prostate ellipse formula. Median PSA density was 0.37, with a range 0.01-6.7. Biochemical failure was defined as three consecutive rises in serum PSA, regardless of the magnitude of elevation. 4-year biochemical disease-free survival (BDFS) for patients with PSAD < or = 0.3 was 60%, compared with 22% for patients with PSAD > 0.3 (p = < 0.001). In a multivariate analysis, **pre-treatment** PSA (p = < 0.001), Gleason score (p = 0.002), and stage (p = 0.03) were independent predictors of BDFS, while PSAD was not an important prognosticator (p = 0.62). **Pre-treatment** serum PSA is the most important prognosticator of BDFS, following external beam radiotherapy, for patients with prostate cancer. PSA density did not predict treatment outcome.

L137 ANSWER 18 OF 29 MEDLINE on STN
ACCESSION NUMBER: 1998105969 MEDLINE
DOCUMENT NUMBER: 98105969 PubMed ID: 9445191
TITLE: Calculated prostate carcinoma volume: The optimal predictor of 3-year prostate specific antigen (PSA) failure free survival after surgery or radiation therapy of patients with **pretreatment** PSA levels of 4-20 nanograms per milliliter.
AUTHOR: D'Amico A V; Whittington R; Kaplan I; Beard C; Schultz D; Malkowicz S B; Wein A; Tomaszewski J E; Coleman C N
CORPORATE SOURCE: Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA 02215, USA.
SOURCE: CANCER, (1998 Jan 15) 82 (2) 334-41. Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980210

AB BACKGROUND. In this study, the authors evaluated whether a clinically relevant stratification of prostate specific antigen (PSA) failure free survival (bNED) after definitive local therapy could be made for patients with prostate carcinoma clinically classified as T1 or T2 and **pretreatment** PSA levels of 4-20 ng/mL. METHODS. Multivariate Cox

regression analysis and Kaplan-Meier analysis were performed for clinically localized prostate carcinoma patients who presented with PSA levels of 4-20 ng/mL. Three hundred forty-eight of the patients were managed definitively with conventional external beam radiation therapy (median dose, 67 gray), whereas 547 of the patients were managed definitively with a radical retropubic prostatectomy. The outcome tested was time to posttreatment PSA failure. The clinical predictors evaluated included the standard paradigm (PSA, biopsy Gleason score, and clinical stage); type of local therapy; and a newly defined factor, the calculated prostate cancer volume (cV[Ca]). RESULTS. Time to posttreatment PSA failure was equivalent (P = 0.52) independent of the type of local therapy. The cV(Ca) (P < 0.0001), **pretreatment** PSA (P = 0.003), and clinical classification of T2c (P = 0.04) remained significant predictors of time to posttreatment PSA failure in multivariate analysis. CONCLUSIONS. The staging system described herein, which is based on cV(Ca) and PSA, may optimize patient selection for definitive local therapy and entry onto randomized clinical trials examining the use of adjuvant hormonal or chemotherapy in patients with clinically localized disease who present with PSA levels of 4-20 ng/mL. Validation of this staging system by other investigators is currently underway.

L137 ANSWER 19 OF 29 MEDLINE on STN
ACCESSION NUMBER: 97428009 MEDLINE
DOCUMENT NUMBER: 97428009 PubMed ID: 9284197
TITLE: Analysis of the local control in lymph-node staged localized prostate cancer treated by external beam radiotherapy, assessed by digital rectal examination, serum prostate-specific antigen and biopsy.
AUTHOR: Borghede G; Aldenborg F; Wurzinger E; Johansson K A; Hedelin H
CORPORATE SOURCE: Department of Oncology, Sahlgrenska Hospital, Goteborg University, Sweden.
SOURCE: BRITISH JOURNAL OF UROLOGY, (1997 Aug) 80 (2) 247-55. Journal code: 15740090R. ISSN: 0007-1331.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 19971008
Entered Medline: 19970922

AB OBJECTIVE: To describe local disease control after radical external beam radiotherapy of prostatic carcinoma, as judged by digital rectal examination (DRE), transrectal ultrasonography (TRUS)-guided biopsies and estimates of serum prostate-specific antigen (PSA). PATIENTS AND METHODS: The study comprised 175 patients (mean age 67.5 years, range 49-82; > 90% aged > or = 60 years) with localized prostatic carcinoma (T1-T3C, N0, M0) who underwent external beam radiation therapy (70 Gy), and were then regularly followed with a DRE, measurements of serum PSA and TRUS-guided biopsies to determine the outcome. RESULTS: The DRE revealed four patients with evidence of residual cancer in the prostate and biopsies showed no evidence of residual cancer in 131 (75%) of the patients. There was no correlation of residual cancer with tumour stage or grade but tumour size, as estimated by TRUS, correlated with the results of the biopsy. The nadir serum PSA level was < or = 1.0 ng/mL in 116 (66%) of the patients, of whom 76 (43%) had a nadir serum PSA level of < or = 0.5 ng/mL. The median time to the nadir level was 11 months. Serum PSA progression (> 4.0 ng/mL) at the latest PSA measurement after reaching the nadir occurred in 13% of the patients with a nadir PSA of < or = 0.5 ng/mL and in 25 of the 29 (86%) patients with a nadir serum PSA > 2.0 ng/mL. Cox regression analysis showed that tumour size and rectal irradiation dose were the most important factors for local control. CONCLUSIONS:

Radiotherapy is effective in achieving local control in small prostate cancer tumours but less effective in large tumours. Tumour size and dorsal extension of the irradiated target, the rectal dose, were the two important factors for local control. A serum PSA level of < or = 1.0 ng/mL was associated with a higher chance of prolonged disease control.

L137 ANSWER 20 OF 29 MEDLINE on STN
ACCESSION NUMBER: 96224909 MEDLINE
DOCUMENT NUMBER: 96224909 PubMed ID: 8635111
TITLE: Prostate specific antigen findings and biopsy results following interactive ultrasound guided transperineal brachytherapy for early stage prostate carcinoma.
AUTHOR: Stock R G; Stone N N; DeWyngaert J K; Lavagnini P; Unger P D
CORPORATE SOURCE: Dpartment of Radiation Oncology, Mount Sinai School of Medicine, New York, New York 10029, USA.
SOURCE: CANCER, (1996 Jun 1) 77 (11) 2386-92.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960719
Last Updated on STN: 19970203
Entered Medline: 19960705

AB BACKGROUND. Interactive, transrectal, ultrasound-guided transperineal implantation is a new technique for performing permanent brachytherapy implants of the prostate. Prostate specific antigen (PSA) findings, biopsy results, and morbidity are examined to demonstrate its efficacy and safety in treating early stage prostate carcinoma. METHODS. Ninety-seven patients underwent permanent implants for classifications T1 to T2 adenocarcinoma of the prostate gland with a median follow-up of 18 months (range: 6-51 months). Seventy-nine patients had negative laparoscopic pelvic lymph node dissections prior to implantation. Patients with positive lymph nodes were not implanted. The radioactive isotope used was I-125 in 71 patients and Pd-103 in 26 patients. RESULTS. PSA failure was defined as two consecutive increases in PSA above the nadir level. The actuarial freedom from PSA failure (FFPF) at 2 years was 76% for the entire group. Stage significantly affected FFPF. Patients classified as T1b to T2a (35) had a FFPF of 91% at 2 years compared with 68.5% for patients classified as T2b to T2c (62) (P = 0.04). The **pre-treatment** PSA also significantly affected FFPF. Patients with PSA values of < or = 10 ng/mL (44) had a FFPF of 83% at 2 years. A similar rate of 82% was found in patients with PSA values of 10.1 to 20 ng/mL (29). Patients with PSA values > 20 ng/mL (24) had a significantly poorer FFPF at 2 years of 58% (P = 0.02). The PSA values of patients free from a PSA failure (82) ranged from 0.1 to 12.9 ng/mL with a median of 0.8 ng/mL. Transrectal prostate biopsies were performed 18 to 36 months posttreatment in 39 patients. Negative biopsies were found in 74% (29/39) of cases. The procedure was associated with an actuarial preservation of erectile function rate and sexual potency at 2 years of 96% and 79%, respectively. There were no cases of urinary incontinence or radiation cystitis. Associated morbidity included urinary retention requiring catheterization in 4% of the patients, outlet obstruction requiring a transurethral resection of the prostate in 2% and Grade 2 rectal complications in 1%. CONCLUSIONS. Interactive, ultrasound-guided transperineal brachytherapy results in a low PSA failure rate, high negative biopsy rate, and is associated with low morbidity and preservation of erectile function.

L137 ANSWER 21 OF 29 MEDLINE on STN
ACCESSION NUMBER: 96185373 MEDLINE

DOCUMENT NUMBER: 96185373 PubMed ID: 8608486
TITLE: The results of radical prostatectomy at a community hospital during the prostate specific antigen era.
AUTHOR: Smitt M C; Heltzel M
CORPORATE SOURCE: Department of Radiation Oncology, Stanford University Medical Center, CA 94305, USA.
SOURCE: CANCER, (1996 Mar 1) 77 (5) 928-33.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960605
Last Updated on STN: 19960605
Entered Medline: 19960528

AB BACKGROUND: The use of radical prostatectomy in the treatment of prostate cancer has increased with the advent of prostate specific antigen (PSA) screening. Few series have examined the relapse rates after prostatectomy relative to **pre-treatment** prognostic factors, such as preoperative PSA and Gleason scores. The characteristics and outcome of patients diagnosed with prostate cancer and treated with radical prostatectomy at community hospitals in the prostate specific antigen era have not been described in detail. METHODS: The tumor registry records were obtained for all patients diagnosed with prostate cancer and treated with radical prostatectomy at Washington Hospital, Fremont, CA, from 1990 through 1993. The clinical and pathologic characteristics, including the original pathology report, for the 100 patients were reviewed by a single physician. Relapse was defined by the persistence or appearance of a PSA value greater than 0.2 ng/mL (Hybritech, Inc., San Diego, CA) following surgery or by clinical evidence of recurrent disease. Crude and actuarial probabilities of relapse were analyzed relative to **pre-treatment** PSA values, Gleason score, pathologic stage, and surgical margin status. The median follow-up time was 2.5 years. RESULTS: The pT-classification distribution of the 100 cases was as follows: T1, 4%; T2A, 14%; T2B, 11%; T2C, 49%; T3A, 8%; T3B, 2%; T3C, 6%; and N+, 6%. **Pretreatment** PSA values were less than or equal to 4 ng/mL for 10 patients, greater than 4 to 10 ng/mL for 38 patients, greater than 10 to 20 ng/mL for 27 patients, and greater than 20 ng/mL for 13 patients. The value was unknown for 12 patients. The Gleason score was less than or equal to 5 for 40%, 6 for 17%, 7 for 31%, and 8 to 10 for 12%. Positive surgical margins were noted in 30% of the patients. The actuarial probability of overall survival and freedom from relapse for the entire group of patients at 3 years was 95% and 73%, respectively. **Pre-treatment** PSA values greater than 20 ng/mL, Gleason score greater than or equal to 7, and pT3 classification were significant predictors of relapse in univariate analysis. Preoperative PSA greater than 20 ng/mL and Gleason score were significant prognostic factors in multivariate analysis. Pathologic margin status was not a significant predictor of relapse in this experience. CONCLUSIONS: Short-term relapse rates are high among those patients with preoperative PSA values greater then 20 ng/mL or Gleason scores greater than or equal to 7. Overall results of radical prostatectomy at this community hospital were similar to those reported at referral centers.

L137 ANSWER 22 OF 29 MEDLINE on STN
ACCESSION NUMBER: 95364042 MEDLINE
DOCUMENT NUMBER: 95364042 PubMed ID: 7543606
TITLE: Prostate specific antigen based disease control following ultrasound guided 125iodine implantation for stage T1/T2 prostatic carcinoma.
AUTHOR: Blasko J C; Wallner K; Grimm P D; Ragde H
CORPORATE SOURCE: Tumor Institute Group, Northwest Tumor Institute, Seattle,

Washington 98133, USA.
SOURCE: JOURNAL OF UROLOGY, (1995 Sep) 154 (3) 1096-9.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19960129
Entered Medline: 19950911

AB PURPOSE: We report the prostate specific antigen (PSA) based recurrence-free survival rate after 125iodine (125I) implantation for early stage prostatic carcinoma. MATERIALS AND METHODS: A total of 197 patients with clinical stage T1 and T2 prostatic carcinoma underwent outpatient 125I seed implantation. Followup was 1 to 7 years (median 3). **Pretreatment** serum PSA levels were elevated (greater than 4.0 ng./ml.) in 138 patients (70%). There were 105 well differentiated (Gleason score 2 to 4), 87 moderately differentiated (Gleason score 5 to 6) and 5 indeterminate tumors. The prescribed minimum prostatic dose was 160 Gy. The total dosage of 125I implanted ranged from 15 to 62 mCi. (median 37). Staging lymph node dissection and seminal vesicle biopsies were not routinely performed. RESULTS: Among 138 patients with an elevated PSA level before implantation and no prior hormonal treatment, the PSA value returned to normal in 98% and decreased to less than 1.0 ng./ml. in 82% within 24 months of treatment. In 97% of those 138 patients the PSA level decreased to less than 1.0 ng./ml. at 48 months after implantation. Of 8 patients with an increasing PSA value 5 also had clinically evident failure. The actuarial rate of chemical (increasing PSA) or clinical failure at 5 years following implantation was 7%, with 15 patients still at risk at 5 years. There was a trend for higher failure rates among patients with higher **pretreatment** PSA levels ($p = 0.57$), Gleason scores 5 and 6 versus 2 to 4 ($p = 0.51$) or higher stage of disease ($p = 0.17$). CONCLUSIONS: There is a high rate of clinical and chemical freedom from progression following 125I implantation for select patients with early stage prostatic carcinoma.

L137 ANSWER 23 OF 29 MEDLINE on STN
ACCESSION NUMBER: 95270457 MEDLINE
DOCUMENT NUMBER: 95270457 PubMed ID: 7538499
TITLE: Prostate-specific antigen for **pretreatment** prediction and posttreatment evaluation of outcome after definitive irradiation for prostate cancer.
COMMENT: Comment in: Int J Radiat Oncol Biol Phys. 1995 May 15;32(2):545-6
AUTHOR: Kuban D A; el-Mahdi A M; Schellhammer P F
CORPORATE SOURCE: Eastern Virginia Medical School, Department of Radiation Oncology, Norfolk.
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (1995 May 15) 32 (2) 307-16.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950629
Last Updated on STN: 19960129
Entered Medline: 19950621

AB PURPOSE: This study was undertaken to assess the predictive value of **pretreatment** prostate-specific antigen (PSA) and the difference between clinical and PSA disease-free status in patients with long-term

follow-up after irradiation for prostatic carcinoma. Comparison of the distribution of prognostic factors between surgical and radiation series was also made. METHODS AND MATERIALS: From 1975-1989, 652 patients with clinical Stage A2-C prostatic adenocarcinoma were definitively irradiated using external beam therapy. One hundred and fifty patients with banked serum and up to 14 years follow-up have **pretreatment** PSA levels and 355 patients with up to 17 years follow-up have posttreatment values. Treatment failure was analyzed by tumor stage, grade, and four **pretreatment** PSA categories. Disease-progression was evaluated by clinical and biochemical (PSA) endpoints. Prognostic factors were compared to two surgical series. RESULTS: A significant difference was seen in clinical and PSA disease-free (PSA < or = 4.0 ng/ml) status based on tumor grade, stage, and **pretreatment** PSA category. Although the expected clinical outcome has been well-documented previously, results based on posttreatment PSA levels show 5-year disease-free survivals reduced by 10-16% and 10-year survivals lessened by 15-39% depending upon the particular tumor grade and stage. The earlier stage, lower grade tumors showed the largest difference between clinical and biochemical recurrence rates at the longest interval from treatment. Even more notable were the differences in the clinical and PSA disease-free rates based on the **pretreatment** PSA level. Comparing the irradiated patients to two surgical series showed that the former had a larger percentage of more advanced stage tumors with more unfavorable PSA levels as compared to prostatectomy patients. CONCLUSION: With long-term follow-up, the **pretreatment** PSA level continues to be a powerful predictor of clinical and biochemical outcome in patients irradiated for apparently localized prostate cancer. Differences between clinical and PSA outcome can be considerable, but oftentimes clinically insignificant. The distribution of prognostic factors between radiation and prostatectomy series seems to favor the latter.

L137 ANSWER 24 OF 29 MEDLINE on STN
ACCESSION NUMBER: 95185022 MEDLINE
DOCUMENT NUMBER: 95185022 PubMed ID: 7533459
TITLE: Radiation therapy for T1 and T2 prostate cancer: prostate-specific antigen and disease outcome.
AUTHOR: Zagars G K; Pollack A
CORPORATE SOURCE: Department of Radiotherapy, University of Texas M.D. Anderson Cancer Center, Houston.
CONTRACT NUMBER: CA 06294 (NCI)
CA16672 (NCI)
SOURCE: UROLOGY, (1995 Mar) 45 (3) 476-83.
Journal code: 0366151. ISSN: 0090-4295.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950419
Last Updated on STN: 19960129
Entered Medline: 19950406

AB OBJECTIVES. To evaluate disease outcome using serum prostate-specific antigen (PSA) as an outcome measure in patients with T1 or T2 prostate cancer treated with radiation therapy in the PSA era. METHODS. We reviewed the outcome for 461 patients with T1 (n = 205) or T2 (n = 256) prostate cancer followed for a median of 31 months after radiation therapy as the sole initial treatment. Univariate and multivariate analyses were used to delineate significant prognostic factors. RESULTS. The freedom from relapse or rising PSA rate was 70% at 6 years and the survival rate was 83%. Although T stage, Gleason grade, serum prostatic acid phosphatase level, and serum PSA level were each significant determinants of outcome in univariate analysis, **pretreatment** PSA level was the only clearly independent covariate (P < 0.0001) in multivariate

analysis. The 5-year actuarial freedom from relapse or from rising PSA levels is shown according to the **pretreatment** PSA level: 4 ng/mL or less (117 patients), 91%; more than 4 but 10 ng/mL or less (169 patients), 69%; more than 10 but 20 ng/mL or less (118 patients), 62%; and more than 20 ng/mL (57 patients), 38%. PSA doubling times in 75 patients with rising post-treatment profiles ranged from 1.3 to 78.2 months (mean, 14.4; median 11.3). Faster doubling times correlated significantly with adverse **pretreatment** prognostic factors (high-grade, high **pretreatment** PSA, and aneuploidy). To date, the survival rate of patients with rising PSA profiles was not depressed below the expected. CONCLUSIONS. Radiation therapy is an acceptable modality for treating T1 or T2 disease and produces results comparable to those following radical prostatectomy when patients are stratified according to their **pretreatment** PSA value. The rapid PSA doubling times observed in patients with relapsing disease are more consistent with a "selective" rather than an "aggravation" mechanism.

L137 ANSWER 25 OF 29 MEDLINE on STN
ACCESSION NUMBER: 95147034 MEDLINE
DOCUMENT NUMBER: 95147034 PubMed ID: 7531222
TITLE: Localized prostate cancer treated by external-beam radiotherapy alone: serum prostate-specific antigen--driven outcome analysis.
AUTHOR: Lee W R; Hanks G E; Schultheiss T E; Corn B W; Hunt M A
CORPORATE SOURCE: Fox Chase Cancer Center, Department of Radiation Oncology, Philadelphia, PA 19111.
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (1995 Feb) 13 (2) 464-9. Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950316
Last Updated on STN: 19960129
Entered Medline: 19950306

AB PURPOSE: To determine the 5-year rate of survival with no evidence of disease (NED) using strict biochemical criteria in men with prostate cancer treated by external-beam radiotherapy alone and to examine possible clinical and treatment factors that predict the likelihood of NED survival. MATERIALS AND METHODS: Five hundred men with clinically localized prostate cancer consecutively treated with external-beam radiotherapy alone with no prior, concomitant, or adjuvant endocrine therapy were identified. All patients had serial serum prostate-specific antigen (PSA) values determined after treatment and 451 patients had **pretreatment** PSA values determined. The median follow-up duration is 20 months (range, 2 to 72; mean, 36). RESULTS: The 5-year rate of overall survival in this group of patients was 80%. The 5-year rate of survival without clinical evidence of disease (cNED) was 72%. The 5-year rate of survival without evidence of clinical, radiographic, or biochemical relapse (bNED) was 51%. Multivariate analysis demonstrated that a **pretreatment** serum PSA level < or = 15 ng/mL was the most important predictor of bNED survival (P < .0001). Patients with early-stage (T1, T2a/b) tumors and a **pretreatment** serum PSA less than 15 ng/mL had a 3-year rate of bNED survival of 86%. The rate of bNED survival for patients with a **pretreatment** PSA level greater than 15 ng/mL was 38% at 3 years. CONCLUSION: **Pretreatment** serum PSA level is the most important predictor of treatment outcome in this group of patients treated with definitive radiotherapy alone. External-beam radiation alone can produce acceptable early rates of bNED survival in patients with clinically organ-confined tumors and a **pretreatment** PSA level < or = 15 ng/mL. To produce acceptable results in those patients with **pretreatment** PSA levels more than 15 ng/mL,

effective adjuvant treatments in addition to aggressive local treatments are necessary.

L137 ANSWER 26 OF 29 MEDLINE on STN
ACCESSION NUMBER: 95018793 MEDLINE
DOCUMENT NUMBER: 95018793 PubMed ID: 7523725
TITLE: Prostate specific antigen as an outcome variable for T1 and T2 prostate cancer treated by radiation therapy.
COMMENT: Comment in: J Urol. 1994 Nov;152(5 Pt 2):1773-4
AUTHOR: Zagars G K
CORPORATE SOURCE: Department of Radiotherapy, University of Texas M.D. Anderson Cancer Center, Houston.
CONTRACT NUMBER: CA 06294 (NCI)
CA 16672 (NCI)
SOURCE: JOURNAL OF UROLOGY, (1994 Nov) 152 (5 Pt 2) 1786-91.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19960129
Entered Medline: 19941114

AB Between 1987 and 1991, 269 patients with clinical stage T1 or T2, N0 or Nx adenocarcinoma of the prostate underwent external beam radiation therapy as the sole initial treatment and were followed with serial prostate specific antigen (PSA) levels for 9 to 73 months (mean 33, median 30). Of the patients 26 had clinical evidence of disease relapse, 58 had an increasing PSA profile and 62 had either relapse or an increasing PSA. The actuarial incidence of increasing PSA was 30% at 5 years and the incidence of relapse or increasing PSA was 36% at the same time. With relapse or increasing PSA level as an end point, **pretreatment** PSA level, Gleason grade and serum prostatic acid phosphatase level were individually significant covariates. However, in multivariate analysis only **pretreatment** PSA level was significant. The 5-year actuarial rates of relapse or increasing PSA according to **pretreatment** PSA level were 4 ng./ml. or less-14%, greater than 4 to 10 ng./ml.-33%, greater than 10 to 30 ng./ml.-55% and greater than 30 ng./ml.-greater than 80%. Post-irradiation PSA levels at 3 and 6 months provided prognostic information additional to that inherent before treatment. However, the nadir PSA value, achieved typically at 6 to 12 months, was the most significant aspect of posttreatment PSA. Patients with a nadir PSA level of less than 1 ng./ml. fared well, with a 12% incidence of relapse or increasing PSA at 5 years. Nadir values exceeding 1 ng./ml. were associated with an increasing relapse rate as the nadir value increased, and nearly two-thirds of the cases in which the nadir exceeded 4 ng./ml. failed by 2 years. When increasing PSA was used as an end point additional to relapse, the outcome in this series was significantly worse than in an earlier series evaluated without PSA. Comparing these 2 series resulted in an estimate that PSA begins to increase approximately 4 to 5 years before the appearance of clinically overt disease. These results reveal the high significance of **pretreatment** PSA levels, significance of nadir PSA values after treatment, earlier detection of persistent disease by the increasing PSA profile, and the fact that total and permanent eradication of localized prostate cancer is considerably more difficult than traditionally believed. The therapeutic implications of this series, and the implications on the quantity and quality of patient lives await prospective study.

L137 ANSWER 27 OF 29 MEDLINE on STN
ACCESSION NUMBER: 94324125 MEDLINE

treatment in prostatic cancer research.

FILE 'HOME' ENTERED AT 14:34:11 ON 27 FEB 2004

F166

ANSWER 116 OF 42399 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 94120900 EMBASE

DN 1994120900

TI Acute **intravenous** toxicity of dimethyl sulfoxide, polyethylene glycol 400, dimethylformamide, absolute **ethanol**, and benzyl alcohol in inbred mouse strains.

AU Montaguti P.; Melloni E.; Cavalletti E.

CS Via della Liberta km. 0.750,I-20052 Monza, Italy

SO Arzneimittel-Forschung/Drug Research, (1994) 44/4 (566-570).
ISSN: 0004-4172 CODEN: ARZNAD

CY Germany

DT Journal; Article

FS 052 Toxicology

LA English

SL English; German

AB Acute **intravenous** toxicity of some **solvents**, i.e. dimethyl sulfoxide (DMSO), polyethylene glycol 400 (PEG 400), dimethylformamide (DMF), absolute **ethanol** (EtOH) and benzyl alcohol (BeOH), was determined in three inbred (CD2F1, B6D2F1 and C57BL/6N) mouse strains used in many preclinical tests, mainly in oncology and toxicology. Haemolytic and precipitation potential tests in vitro were performed to assess the blood compatibility of the investigated **solvents** and its relationship with the observed symptoms. The single tested **solvents** did not show any major differences in acute toxicity in the three tested strains with the exclusion of DMSO (less toxic in CD2F1) and BeOH and EtOH (less toxic in B6D2F1). The tested dose ranges in the three strains (in ml/kg) were 1.0-5.66 for DMSO, 2.0-8.0 for PEG 400, 1.0-4.0 for DMF, 0.75-4.24 for EtOH, 0.025-0.4 for BeOH. The lowest tested dose was a safe dose and the highest one was the dose causing mortality in no more than half the animals in each group. The in vitro results suggest avoiding the use of BeOH (which also is more toxic than the other **solvents** in the in vivo test) and DMSO and using PEG 400, EtOH and DMF even though the latter induced a body weight decrease in the B6D2F1 mouse strain. As a general conclusion, dilution of these **solvents** in water is suggested to ameliorate their blood compatibility and the use of doses not higher than the lowest dose tested in this study is recommended.